

DNA Methylation and Epigenetic Modifications Linking Obesity, Insulin Resistance, and Cancer Risk

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ABSTRACT

Obesity and insulin resistance are closely interconnected metabolic disorders that significantly elevate the risk of various cancers. Emerging evidence implicates epigenetic modifications, particularly DNA methylation, as pivotal mediators linking these conditions. DNA methylation is a heritable yet reversible epigenetic mechanism that regulates gene expression without altering the underlying DNA sequence. In the context of obesity, aberrant DNA methylation patterns have been identified in genes involved in adipogenesis, inflammation, insulin signaling, and tumorigenesis. Insulin resistance, characterized by impaired glucose uptake and chronic hyperinsulinemia, further exacerbates these epigenetic disruptions, creating a permissive environment for cancer initiation and progression. Additionally, lifestyle and environmental exposures, such as diet, physical activity, and early-life nutritional status, influence DNA methylation signatures and may program long-term disease susceptibility. This review explores the mechanistic roles of DNA methylation in obesity-induced insulin resistance and its downstream impact on cancer development. We discuss key methylated genes and pathways implicated in adipose tissue dysfunction, chronic inflammation, metabolic reprogramming, and cellular proliferation. Furthermore, we highlight recent advances in epigenome-wide association studies (EWAS), emerging biomarkers for early detection, and the potential for epigenetic therapies targeting modifiable methylation patterns. Understanding the epigenetic links between obesity, insulin resistance, and cancer opens new avenues for precision prevention and personalized treatment strategies in at-risk populations.

Keywords: DNA methylation, epigenetics, obesity, insulin resistance, cancer risk, adipose tissue, chronic inflammation

INTRODUCTION

The global prevalence of obesity has escalated dramatically over the past few decades, reaching what many public health organizations consider a global epidemic[1–3]. According to the World Health Organization (WHO), more than 1.9 billion adults worldwide are overweight, and over 650 million are classified as obese. This alarming trend is associated with an increased risk of a multitude of chronic health conditions, including cardiovascular disease, metabolic syndrome, type 2 diabetes mellitus (T2DM), and various forms of cancer[4–6]. The pathophysiological mechanisms linking obesity to these diseases are multifaceted, involving complex interactions among genetic, metabolic, hormonal, and immune factors.

Obesity, particularly central or visceral adiposity, plays a pivotal role in driving insulin resistance, a key feature of T2DM. Insulin resistance occurs when cells in muscle, fat, and the liver become less responsive to insulin, thereby impairing glucose uptake and utilization[7–10]. This dysfunction leads to hyperglycemia and compensatory hyperinsulinemia, which contribute to further metabolic derangement. Furthermore, obesity is recognized as a pro-inflammatory condition due to the excessive release of cytokines and adipokines from hypertrophied adipose tissue. These pro-inflammatory mediators not only exacerbate insulin resistance but also create a microenvironment conducive to carcinogenesis[8, 11–13]. In recent years, the focus has shifted toward understanding the molecular underpinnings that mediate the effects of obesity on disease development, with increasing attention on the role of epigenetics. Epigenetics refers to heritable changes in gene expression that do not involve alterations in the DNA sequence[14–16]. Among the various epigenetic mechanisms, DNA methylation is the most extensively studied. It involves the addition of a methyl group to the 5-carbon of cytosine residues, primarily in CpG dinucleotides, and plays a fundamental role in regulating gene expression, chromatin structure, and genome stability[17, 18]. Emerging evidence indicates that obesity induces significant alterations in DNA methylation patterns, particularly in genes implicated in metabolic regulation, immune

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responses, and cellular proliferation. These epigenetic changes may serve as molecular bridges connecting obesity, insulin resistance, and cancer[19]. Importantly, unlike genetic mutations, epigenetic modifications are dynamic and potentially reversible, influenced by diet, physical activity, environmental exposures, and pharmacological agents. This opens new avenues for preventive and therapeutic strategies aimed at modulating epigenetic marks to mitigate the adverse health outcomes associated with obesity[19].

The concept that epigenetic dysregulation could represent a unifying mechanism linking obesity to both metabolic and oncogenic pathways has garnered substantial interest. DNA methylation profiles have been shown to vary significantly between lean and obese individuals and are associated with differential disease risks[20]. Additionally, obesity-related epigenetic changes in key tissues such as liver, adipose, pancreas, and muscle can persist over time and even across generations, suggesting the involvement of epigenetic memory and transgenerational effects[20].

Understanding the interplay between obesity, DNA methylation, and disease pathogenesis is crucial for the development of biomarkers for early detection, risk stratification, and personalized medicine. It also has significant public health implications, as targeting modifiable epigenetic mechanisms may offer cost-effective interventions for a wide spectrum of chronic diseases. In this context, the exploration of DNA methylation as a mechanistic and therapeutic link among obesity, insulin resistance, and cancer represents a promising frontier in biomedical research.

2. DNA Methylation and Epigenetic Regulation

DNA methylation is one of the most fundamental and well-characterized epigenetic modifications, playing a central role in gene expression regulation, genomic imprinting, X-chromosome inactivation, and the suppression of transposable elements[21]. This process involves the covalent addition of a methyl group to the 5-position of cytosine residues within CpG dinucleotides, a reaction catalyzed by DNA methyltransferases (DNMTs), including DNMT1, DNMT3A, and DNMT3B. DNMT1 maintains methylation patterns during DNA replication, while DNMT3A and DNMT3B are responsible for de novo methylation during embryonic development and cellular differentiation[21, 22].

In gene promoter regions, DNA methylation typically acts as a repressive mark by interfering with the binding of transcription factors and recruiting methyl-CpG-binding domain proteins that further condense chromatin structure, thus silencing gene expression. However, the impact of methylation depends on the genomic context; for example, gene body methylation is often associated with active transcription[23]. In the context of health and disease, DNA methylation is a dynamic process that can be modulated by various environmental and lifestyle factors, including diet, exercise, smoking, alcohol consumption, and exposure to toxins or stress. In obesity, numerous studies have documented aberrant DNA methylation patterns in key metabolic tissues such as adipose tissue, liver, skeletal muscle, and pancreatic islets[23]. These changes often involve genes regulating lipid metabolism (e.g., FASN, SREBF1), glucose homeostasis (e.g., IRS1, GLUT4), and inflammation (e.g., TNF- α , IL-6). Such epigenetic alterations contribute to dysregulated energy homeostasis, insulin resistance, and chronic inflammation—hallmarks of obesity-related metabolic dysfunction[24].

Importantly, DNA methylation also plays a critical role in cancer development and progression. One of the earliest and most common epigenetic alterations observed in cancer is the hypermethylation of promoter CpG islands in tumor suppressor genes, leading to their transcriptional silencing[25]. Simultaneously, global hypomethylation of the genome, particularly in intergenic and repetitive regions, can result in chromosomal instability and the activation of oncogenes. Thus, the duality of hyper- and hypomethylation underlines the complexity of epigenetic regulation in oncogenesis[26]. The link between epigenetic dysregulation and metabolic disease becomes more compelling considering the overlap in affected pathways. Chronic inflammation and oxidative stress, both prominent in obesity, can influence the activity of DNMTs and ten-eleven translocation (TET) enzymes that mediate DNA demethylation. Additionally, methyl donor availability through one-carbon metabolism (e.g., folate, methionine, vitamin B12) can modulate methylation status, providing a direct connection between nutrient intake and epigenetic marks.[26]

Crucially, these epigenetic modifications are not only markers of disease but may also contribute causally to pathogenesis. For instance, altered methylation in genes such as PPAR γ or LEP (leptin) can impair adipocyte differentiation or hormone secretion, further perpetuating metabolic imbalance[27]. In cancer, obesity-associated DNA methylation may prime the epigenome for malignant transformation by altering the expression of genes involved in cell cycle regulation, DNA repair, and apoptosis[27].

Given the reversibility of DNA methylation, it represents a promising therapeutic target. Pharmacologic agents such as DNMT inhibitors (e.g., azacitidine, decitabine) have shown efficacy in hematological malignancies, though their use in solid tumors or metabolic diseases remains under investigation[28]. Moreover, lifestyle interventions like weight loss, dietary modifications, and physical activity have been shown to partially reverse aberrant DNA methylation patterns, suggesting that epigenetic plasticity can be harnessed for disease prevention and management.

3. Obesity-Induced Epigenetic Alterations

Obesity induces widespread epigenetic changes, particularly in DNA methylation, across multiple tissues and developmental stages. These changes are driven by a confluence of biological stressors associated with excessive This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited

caloric intake, adipose tissue hypertrophy, oxidative stress, and chronic inflammation[29]. The altered metabolic milieu in obesity significantly influences the activity of DNA methylation enzymes and reshapes the epigenetic landscape of key regulatory genes, thereby contributing to the pathogenesis of insulin resistance, type 2 diabetes, and cancer[29].

Numerous human and animal studies have shown that obese individuals exhibit distinctive DNA methylation profiles compared to their lean counterparts[30]. These differences are often tissue-specific but can also be detected in peripheral blood leukocytes, suggesting systemic epigenetic reprogramming. In adipose tissue, hypermethylation of adipogenesis-related genes such as *PPARG* (peroxisome proliferator-activated receptor gamma) and *C/EBPα* (CCAAT/enhancer-binding protein alpha) impairs the differentiation of preadipocytes into mature adipocytes[31]. This dysfunction results in ectopic fat deposition, lipotoxicity, and systemic insulin resistance.

Inflammatory pathways are also epigenetically modulated in obesity. Key pro-inflammatory cytokine genes, including *TNF-α* and *IL-6*, often display hypomethylation, leading to their overexpression and the establishment of a chronic low-grade inflammatory state[32]. This inflammation not only disrupts insulin signaling in peripheral tissues but also primes the microenvironment for carcinogenesis by promoting DNA damage, cellular proliferation, and angiogenesis[32]. The insulin signaling cascade itself is subject to epigenetic regulation. Genes such as *IRS1* (insulin receptor substrate 1) and *GLUT4* (glucose transporter type 4) have been reported to undergo hypermethylation in obese subjects, resulting in impaired glucose uptake and insulin sensitivity[33]. Additionally, genes involved in mitochondrial function and oxidative phosphorylation may be epigenetically silenced, contributing to metabolic inflexibility and energy imbalance. Adipose tissue in obesity becomes not only a storage depot but also an active endocrine organ. It secretes various adipokines, including leptin and adiponectin, which are critical regulators of appetite, energy expenditure, insulin sensitivity, and inflammation[10]. Obesity-induced methylation changes in the *LEP* and *ADIPOQ* genes can alter their expression levels, thereby disrupting systemic metabolic homeostasis. For instance, hypermethylation of the *ADIPOQ* promoter reduces adiponectin expression, leading to increased insulin resistance and cardiovascular risk[10].

One of the most compelling aspects of obesity-induced epigenetic changes is their potential persistence across time and even generations. Epigenetic modifications initiated during prenatal life or early childhood, critical windows of developmental plasticity, may predispose individuals to obesity and metabolic disorders later in life[34]. For example, maternal obesity or a high-fat diet during pregnancy can induce epigenetic changes in fetal tissues, particularly in genes regulating appetite, energy metabolism, and adipogenesis. These alterations may persist into adulthood, establishing an “epigenetic memory” that perpetuates disease risk. Furthermore, these epigenetic changes are not confined to metabolic disease alone but extend to cancer susceptibility[34]. Obesity-related DNA methylation alterations in genes regulating cell proliferation, DNA repair, and apoptosis may act as early events in tumorigenesis. For example, methylation changes in *APC*, *CDKN2A*, and *BRCA1* have been associated with increased cancer risk in obese individuals, particularly in tissues such as the colon, liver, and breast[35].

In sum, obesity-induced DNA methylation changes serve as both indicators and mediators of metabolic dysfunction and oncogenesis. Their reversible nature presents a unique therapeutic window for intervention. Identifying and targeting specific methylation changes through lifestyle modification or pharmacological approaches may provide a viable strategy for preventing or mitigating obesity-associated diseases.

4. Insulin Resistance and Epigenetic Crosstalk

Insulin resistance (IR) is a pathological condition where the body's cells, particularly in skeletal muscle, liver, and adipose tissue, become less responsive to the action of insulin[7, 9, 33]. This insensitivity leads to impaired glucose uptake, increased hepatic glucose production, and a compensatory rise in insulin secretion, often resulting in chronic hyperinsulinemia. While the molecular basis of insulin resistance has been traditionally attributed to genetic predisposition, inflammation, and lipid accumulation, emerging evidence underscores the significant role of epigenetic modifications in modulating insulin sensitivity[36–38].

Epigenetic mechanisms such as DNA methylation, histone modifications, and non-coding RNAs influence the expression of genes involved in insulin signaling pathways[29, 34]. In insulin-resistant individuals, aberrant DNA methylation has been observed in key genes, including insulin receptor substrate 1 and 2 (*IRS1*, *IRS2*), glucose transporters (*GLUT1*, *GLUT4*), and components of the *PI3K/AKT* pathway. These changes can impair downstream insulin signaling, further reducing glucose uptake and utilization. For example, hypermethylation of the *IRS1* promoter leads to its transcriptional repression, thereby disrupting signal transduction from the insulin receptor[22, 27, 39].

Tissues commonly affected by insulin resistance, such as skeletal muscle and liver, exhibit differential methylation patterns in genes critical to metabolic regulation. In the liver, genes like glucokinase (*GCK*), phosphoenolpyruvate carboxykinase (*PEPCK*), and *FOXO1* are often methylated in a manner that disrupts gluconeogenesis and glycogen synthesis. In skeletal muscle, epigenetic modifications can impair fatty acid oxidation and mitochondrial biogenesis, thereby compounding metabolic dysfunction. Chronic hyperinsulinemia

not only maintains a state of insulin resistance but also fosters a mitogenic environment by upregulating insulin-like growth factor 1 (IGF-1) signaling. This growth-promoting axis can contribute to uncontrolled cell proliferation and survival, particularly in a milieu of sustained metabolic stress[40, 41]. When coupled with epigenetic dysregulation such as silencing of tumor suppressor genes and activation of oncogenic pathways this environment becomes conducive to oncogenic transformation. Thus, the interaction between insulin resistance and epigenetic changes forms a vicious cycle, where metabolic dysfunction and aberrant gene expression reinforce each other. Understanding these mechanisms opens avenues for targeted therapies that can modulate epigenetic states to restore insulin sensitivity and prevent downstream pathologies, including cancer.

5. Cancer Risk: The Epigenetic Bridge

The increased cancer risk observed in individuals with obesity and insulin resistance is a complex outcome of hormonal dysregulation, chronic inflammation, oxidative stress, and aberrant cellular signaling. Among the mechanisms that bridge metabolic disturbances and oncogenesis, epigenetic modifications, particularly DNA methylation, stand out as crucial mediators[42, 43]. They serve as a molecular link connecting environmental exposures and metabolic imbalances to persistent alterations in gene expression that favor tumor development. One of the most well-characterized epigenetic events in cancer is the hypermethylation of promoter regions in tumor suppressor genes. In obese, insulin-resistant individuals, genes such as CDKN2A (p16INK4a), RASSF1, and MLH1 are often silenced through methylation, leading to the loss of regulatory checkpoints that normally prevent uncontrolled cell division and DNA damage accumulation[44, 45]. Simultaneously, hypomethylation of oncogenes like MYC and MET results in their overexpression, promoting cell proliferation, migration, and survival—hallmarks of cancer[45]. Inflammation, a chronic feature of obesity, also contributes to the epigenetic landscape of cancer. Pro-inflammatory cytokines such as TNF- α and IL-6 can influence DNA methyltransferase (DNMT) activity, thereby modulating the methylation status of genes involved in inflammation, immune regulation, and cell cycle control. Epigenetic changes in inflammation-related genes can create a tumor-permissive microenvironment that supports angiogenesis, immune evasion, and metastasis[45].

Adipose tissue itself undergoes epigenetic reprogramming in obesity. Methylation changes in genes such as FTO (fat mass and obesity-associated gene), LEP (leptin), and ADIPOQ (adiponectin) alter the secretion profiles of adipokines[46]. Elevated leptin levels in obese individuals stimulate mitogenic and anti-apoptotic pathways via JAK/STAT and PI3K signaling, promoting cancer progression. Conversely, reduced adiponectin, a hormone with anti-inflammatory and tumor-suppressive properties, is associated with increased cancer susceptibility[46].

Collectively, these methylation-driven modifications form a multifaceted epigenetic bridge that connects metabolic dysregulation with oncogenic transformation. They provide not only mechanistic insights but also therapeutic opportunities. Drugs targeting epigenetic enzymes (e.g., DNMT inhibitors) and lifestyle interventions that modify epigenetic marks (e.g., diet, exercise) could be leveraged to mitigate cancer risk in metabolically compromised individuals.

6. Epigenome-Wide Association Studies (EWAS) and Biomarker Discovery

Advancements in high-throughput sequencing and methylation profiling technologies have revolutionized our understanding of the epigenetic underpinnings of complex diseases. Epigenome-Wide Association Studies (EWAS) are at the forefront of this revolution, enabling researchers to systematically map DNA methylation patterns across the genome and associate them with specific disease phenotypes, including obesity, insulin resistance, and cancer[47]. EWAS have identified a multitude of differentially methylated CpG sites in obese and insulin-resistant populations. These epigenetic signatures are often found in genes involved in glucose metabolism, lipid handling, inflammation, and cellular stress responses[48]. For instance, SOCS3 (suppressor of cytokine signaling 3), HIF3A (hypoxia-inducible factor 3 alpha), and TXNIP (thioredoxin-interacting protein) are frequently reported as differentially methylated in studies involving obese and type 2 diabetic individuals. These genes are implicated in insulin signaling suppression, oxidative stress, and energy metabolism—all key factors in metabolic dysfunction[49].

Similarly, in obesity-associated cancers, EWAS have revealed hypermethylation of genes such as MGMT (O6-methylguanine-DNA methyltransferase) and BRCA1, both of which play roles in DNA repair and tumor suppression[50]. These epigenetic alterations can predispose individuals to carcinogenesis by compromising genomic integrity and enabling the accumulation of oncogenic mutations. Beyond their mechanistic implications, these methylation marks serve as promising biomarkers for early disease detection and progression monitoring[50]. Their stability in bodily fluids such as blood and saliva makes them suitable for non-invasive testing. For example, methylated HIF3A in blood samples has been proposed as a predictive biomarker for obesity-related complications. Similarly, hypermethylated BRCA1 detected in circulating tumor DNA (ctDNA) is under investigation for its potential use in early breast cancer diagnosis[51].

Moreover, EWAS findings support the concept of epigenetic plasticity, that is, the potential for reversibility of epigenetic marks through interventions. Lifestyle modifications like caloric restriction, exercise, and bariatric surgery have been shown to partially reverse obesity-associated methylation changes. Pharmacological agents targeting epigenetic enzymes (e.g., DNMT and HDAC inhibitors) are also being explored for their dual role in metabolic regulation and cancer therapy[51, 52].

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In sum, EWAS provides a powerful platform for discovering novel epigenetic biomarkers and therapeutic targets. As the field progresses, integrating EWAS data with transcriptomic, proteomic, and metabolomic analyses will further enhance our ability to develop precision medicine strategies for managing obesity, insulin resistance, and cancer.

7. Therapeutic and Preventive Implications

Given the plasticity of epigenetic marks, targeting DNA methylation offers promising therapeutic avenues. DNMT inhibitors, such as azacytidine and decitabine, are already used in hematologic malignancies and are being explored in solid tumors. In metabolic disorders, emerging data suggest that dietary modifications, exercise, and weight loss can modulate DNA methylation and improve metabolic outcomes.

Early-life epigenetic programming also underscores the importance of maternal nutrition and prenatal care in preventing long-term disease risk. Public health strategies that incorporate epigenetic understanding may enhance the effectiveness of obesity and cancer prevention efforts.

CONCLUSION

DNA methylation serves as a critical link between obesity, insulin resistance, and cancer, integrating genetic susceptibility with environmental exposures. Aberrant methylation patterns in key regulatory genes underpin the pathophysiology of metabolic dysfunction and tumorigenesis. As our understanding of the epigenetic landscape expands, so does the potential for precision medicine approaches that leverage epigenetic biomarkers and therapeutic targets. Future research should focus on longitudinal studies, integrative omics analyses, and translational strategies to harness the full potential of epigenetics in combating obesity-related cancer risk.

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