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REVIEW

EPIGENETIC REGULATION OF ADIPOSE TISSUE: INSIGHTS INTO METABOLIC FUNCTIONS AND DYSFUNCTION

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ABSTRACT

Adipose tissue, the body's primary energy-storing tissue, has additional roles in hormone regulation and thermogenesis. While it has been traditionally examined through the lens of hormonal and nervous system interactions, recent advancements have highlighted the importance of epigenetic modifications in adipose tissue function and dysfunction. This review examines how epigenetic modifications impact the functions of white adipose tissue, brown adipose tissue, and beige adipose tissue, how these alterations contribute to the development of obesogenic memory, and how they indirectly affect the central nervous system to sustain obesity. Additionally, it explores the impact of epigenetic alterations on obesity susceptibility and the outcomes of metabolic diseases such as obesity and type 2 diabetes, following a brief overview of epigenetic modifications, the types of adipose tissue, and their functions. Epigenetic mechanisms such as deoxyribonucleic acid methylation, histone modifications and non-coding ribonucleic acid modulations have a considerable role in adipocyte differentiation, lipid metabolism, and thermogenesis in brown and beige adipose tissue. In white adipose tissue, these modifications are linked to dysregulated lipid storage and metabolic impairments associated with obesity. Brown and beige adipose tissue, adipose tissues responsible for non-shivering thermogenesis, are also regulated by a network of transcription factors and epigenetic regulators that modulate their differentiation and function. Studies have indicated that transgenerational epigenetic inheritance may be a contributing factor to the rising prevalence of metabolic diseases, including non-alcoholic liver disease, obesity, and type 2 diabetes. Furthermore, differential deoxyribonucleic acid methylation patterns in genes associated with obesity and type 2 diabetes have been revealed, offering insights into the mechanisms of these diseases and potential therapeutic targets. Interestingly, bariatric surgery appears to have an effect that resets the obesogenic memory, making it a more effective long-term treatment than conventional weight loss methods. This provides a link between epigenetics and weight loss interventions. Furthermore, the potential role of epigenetics in central nervous system regulation of appetite and energy homeostasis underscores its systemic impact on metabolic pathways using the reward circuitry involved in hedonic regulation. This review emphasizes the significance of epigenetic regulation in adipose tissue functions and its implications for metabolic diseases. The comprehension of these mechanisms serves as a foundation for the development of innovative therapeutic approaches to address the growing prevalence of metabolic diseases, including obesity and diabetes.

Keywords: Adipose tissue, diabetes mellitus, epigenomics, lipogenesis, obesity

INTRODUCTION

Adipose Tissue

Adipose tissue (AT) has traditionally been divided into two types, white AT (WAT) and brown AT (BAT), which are visually distinguished by the color of the tissue (1). These two tissue types exhibit distinct characteristics, resulting in unique physiological roles within the body (Figure 1) (1). WAT represents the most prominent energy reserve in humans, yet it is also responsible for several endocrine functions (2). White adipocytes typically have a spherical shape, and each contains a single large lipid droplet that pushes the other organelles to the side and can grow up to 100 µm (1, 3).

Brown AT is predominantly found during the postnatal period in infants and plays a crucial role in non-shivering thermogenesis (1). This process is driven by the protein uncoupling protein-1

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(UCP-1), which facilitates adenosine triphosphate utilization for heat production (1, 3, 4). Unlike white adipocytes, brown adipocytes are distinguished by their multiple lipid droplets dispersed throughout a larger ellipsoidal-shaped cell rich in mitochondria, which contains iron (1). This gives the cell and the BAT overall a brownish color (1, 3). The adipose cells forming this tissue are typically smaller in size (3). Although it was once believed to exist exclusively during the postnatal period, imaging studies have revealed its presence in adults, particularly in the supraclavicular and thoracic regions (1).

Recently, two additional types of ATs have been identified: beige and pink adipose cells (1). Beige AT (BeAT) displays characteristics of both brown and white fat tissues (Figure 1), which will be elaborated on later (1). Pink AT, on the other hand, has been observed in pregnant rodents and is believed to arise from the reversible transformation of subcutaneous AT into mammary glandular tissue (3). However, studies focusing on this specific tissue type remain limited (3).

Lipid Metabolism and Thermogenesis

Lipid metabolism is a complex network of pathways influenced by internal and external factors. Dysregulation in processes such as adipogenesis, lipolysis, and lipid oxidation is often associated with obesity, diabetes, non-alcoholic fatty liver disease, and cardiovascular disorders (5). AT regulates lipid metabolism by balancing triglyceride storage and breakdown in response to nutritional and hormonal signals, though fat is also stored in visceral organs such as the liver (1, 6).

Adipocytes store triglycerides via two mechanisms: absorbing dietary lipids from the bloodstream as free fatty acids released from circulating triglycerides by lipoprotein lipase (LPL), and de novo lipogenesis, synthesizing fatty acids from acetyl coenzyme A, especially following carbohydrate-rich meals (1, 4). These fatty acids undergo esterification with glycerol to form triglycerides (1, 4). During periods of elevated energy demand, such as fasting or exercise, lipolysis releases fatty acids and glycerol from adipocytes (4). Hormones such as noradrenaline activate lipolysis via β-adrenergic receptors and protein kinase A, which in turn activates hormone-sensitive lipase and adipose triglyceride lipase (4). Insulin exerts an inhibitory effect on lipolysis by reducing cyclic adenosine monophosphate levels (1, 4).

As previously mentioned, BAT differs from WAT by producing heat through non-shivering thermogenesis via UCP-1 (1, 7-9). The activity of BAT is known to increase during periods of cold exposure, which is linked to adaptive thermogenesis (8-10). This may play a role in regulating body weight (9, 10). Additionally, research has shown that leaner individuals tend to have higher BAT activity than those with a higher body mass index (BMI) (9, 10). This further supports the idea that BAT activity may be associated with weight control.

Epigenetic Mechanisms in Gene Regulation

Epigenetics is the study of heritable modifications to gene expression that do not involve changes to the underlying deoxyribonucleic acid (DNA) sequence (11). Nutrition, metabolic abnormalities, physical activity, oxidative stress, inflammation, and medications are among the environmental factors identified as contributors to these alterations (11). Such alterations may be reversed, but they may also be transmitted to subsequent generations (11). Epigenetic data is stored in chromatin, which is composed of multiple nucleosome units (DNA-wrapped histone

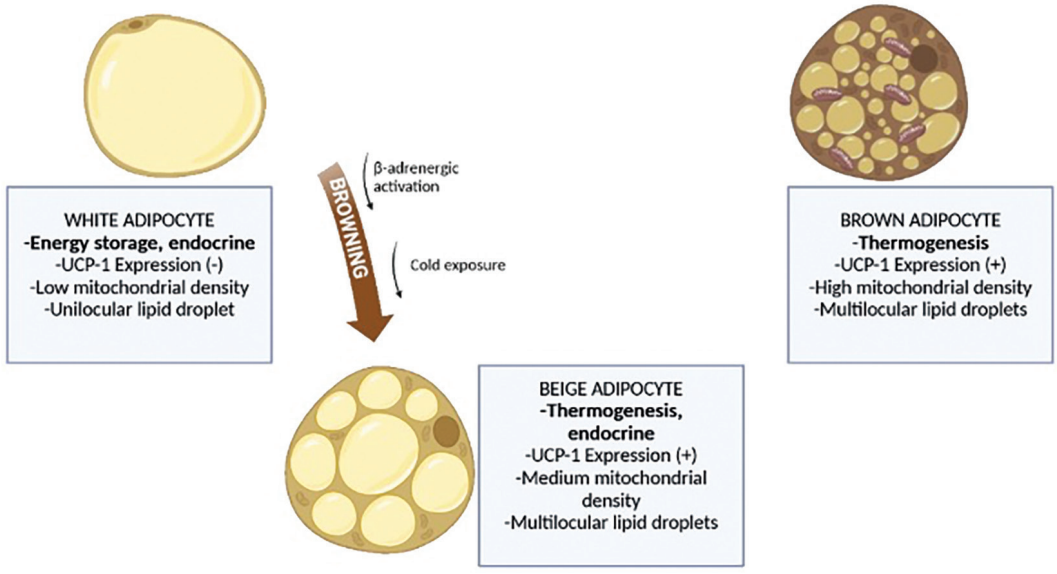

Figure 1: White, brown and beige adipocytes. White adipocytes primarily serve as the body's main energy storage while also playing key endocrine roles (2). In contrast, brown adipocytes are responsible for non-shivering thermogenesis (1-4). Beige adipocytes exhibit characteristics of both white and brown adipocytes (1). These cells originate from white adipocytes and are activated by factors such as β-adrenergic stimulation and cold exposure (7). This figure was created using the program: BioRender.

UCP-1: Uncoupling protein 1

octamers) (11). The chromatin structure is of great importance in identifying the transcriptional state of DNA (11). Unlike the euchromatin region, which is more open and transcriptionally active, the heterochromatin region of DNA is densely packed and transcriptionally inactive (11). These chromatin states are regulated by epigenetic modifications (11). The most prominent epigenetic modifications include DNA methylation, histone modifications, and non-coding ribonucleic acid (ncRNA) modulations (Figure 2), which are briefly described below (11-13).

DNA methylation is the process in which a methyl group from S-adenosyl methionine is added to a cytosine residue in DNA, a reaction catalyzed by DNA methyltransferases (DNMTs) (11). This modification inhibits transcription by preventing DNA-binding proteins, from accessing the methylated site (11). DNA methylation occurs predominantly at cytosine followed by guanine, commonly referred to as "CpG methylation" (11, 12). Among the other epigenetic alterations, DNA methylation is considered to be the key epigenetic mechanism (13). In histone acetylation, histone acetyltransferases (HATs) add an acetyl group to the lysine residues on the N-terminal tails of histones, enhancing transcriptional activity (14). Histone methylation is the process by which histone methyltransferases (HMTs) transfer the methyl group to the N-terminal of the lysine and arginine residues of histone tails (11, 15). Unlike histone acetylation, histone methylation can either stimulate or inhibit transcription (15). Histone crotonylation can either activate or suppress gene transcription by adding a crotonyl group to the lysine residues of histones (11). Histone ubiquitination is the process in which the E1, E2, and E3 ligases attach ubiquitin molecules to the lysine residues of histones, marking them for proteasomal degradation (11). Histone phosphorylation occurs when serine, threonine, or tyrosine residues on histone proteins are modified by histone kinases (11). This modification can alter the structure and function of histone tails, influencing chromatin dynamics and gene expression. In addition to influencing adaptors, transcription factors, chromatin-modifying enzymes, repressors, and transcription regulation, these modifications to the amino-terminal tails of histones also affect how histones interact with DNA (11, 16). Furthermore, these modifications are believed to create a "histone code" on the N-terminal histone tails that signals proteins or complexes to "read" and use to initiate signaling pathways (14). The hypothesis "histone code" states that post-translational changes to these histone proteins have a significant impact on DNA transcription (17). As a result, histones are crucial for the epigenetic control of gene transcription and may also be involved in nuclear signaling complexes (14).

Non-coding RNAs, which are not translated into proteins, also play a role in gene regulation (11). These include microRNA (miRNA), long non-coding RNA (lncRNA), and small interfering RNA (siRNA) (11). Non-coding RNAs (ncRNAs) were previously believed to regulate gene expression solely at the post-transcriptional level; however, recent studies indicate their growing significance in epigenetic regulation (18).

MicroRNAs typically interact with the 3' untranslated region of target messenger RNAs (mRNA), leading to mRNA degradation and translational repression (19, 20). However, miRNAs have also been observed to bind other regions, such as the 5' untranslated region, coding sequences, and gene promoters (20). Additionally, miRNAs contribute to epigenetic modifications (21). For instance, at least two miRNAs, which are downregulated by oncogenes or other tumorigenic factors, appear to target the histone methyltransferase enhancer of zeste homolog 2 (EZH2), ultimately leading to its overexpression (21). Similarly, miR-214 has been shown to suppress EZH2 expression, thereby promoting skeletal muscle differentiation (21). Furthermore, miRNAs influence DNA methylation by modulating DNA methyltransferases (18). Notably, the miR-29 family (including miR-29a, miR-29b, and miR-29c) exhibits reduced expression in non-small cell carcinoma, while DNMT3a and DNMT3b are significantly upregulated (18).

Long non-coding RNAs represent a class of regulatory RNA molecules typically exceeding 200 nucleotides in length (18). These molecules have critical roles in the cytoplasm and beyond, including roles in translation regulation, metabolism, and signaling (22). lncRNAs often possess modular structures enriched in repetitive elements, which have been increasingly recognized as functionally significant (22). Early research on genomic imprinting and X chromosome inactivation identified the lncRNAs H19 and X-inactive specific transcript as key players in epigenetic regulation (18). Several studies have reported elevated H19 expression in cancer cell lines and patient-derived samples, suggesting its potential role in tumorigenesis (23). In gastric cancer cells, H19 upregulation has been linked to increased miR-675 expression, with both genes promoting cell proliferation and inhibiting apoptosis, whereas their suppression has the opposite effect (23).

Small interfering RNAs silence gene expression through RNA interference (RNAi) pathways, operating at both the transcriptional and post-transcriptional levels (24). RNAi is a biological process in which double-stranded RNA triggers gene silencing by directing the degradation of complementary mRNA (25). Within this mechanism, Argonaute (Ago) proteins, in association with siRNAs, form the core components of RNA-induced silencing complexes (RISC) and RNA-induced transcriptional silencing complexes (RITS), both of which are essential effectors of RNAi (24). The guide strand of siRNA base-pairs with its target RNA, enabling precise cleavage of the target transcript (24).

In addition to miRNAs and siRNAs, another class of small ncRNAs, known as piwi-interacting RNAs (piRNAs), has been implicated in epigenetic regulation (26). The Piwi protein functions as an epigenetic regulator by binding to genomic polycomb group (PcG) response elements in conjunction with PcG proteins, leading to the silencing of homeobox genes (18). This association suggests that piRNAs play a crucial role in epigenetic regulation (18).

Epigenetics and White Adipose Tissue

As with many other organs and tissues, it is inevitable that epigenetics will have a considerable impact on the development and functions of AT. In the context of WAT, recent interest has focused on alterations in the epigenome, particularly in relation to obesity and its associated comorbidities (Figure 3).

Epigenetics and Adipose Tissue Memory

People with obesity often have challenges with weight regain after losing weight (27). This phenomenon, known as weight recidivism, is frequently attributed to difficulties in maintaining dietary and physical activity routines (28). However, it is well-established that a wide range of physiological

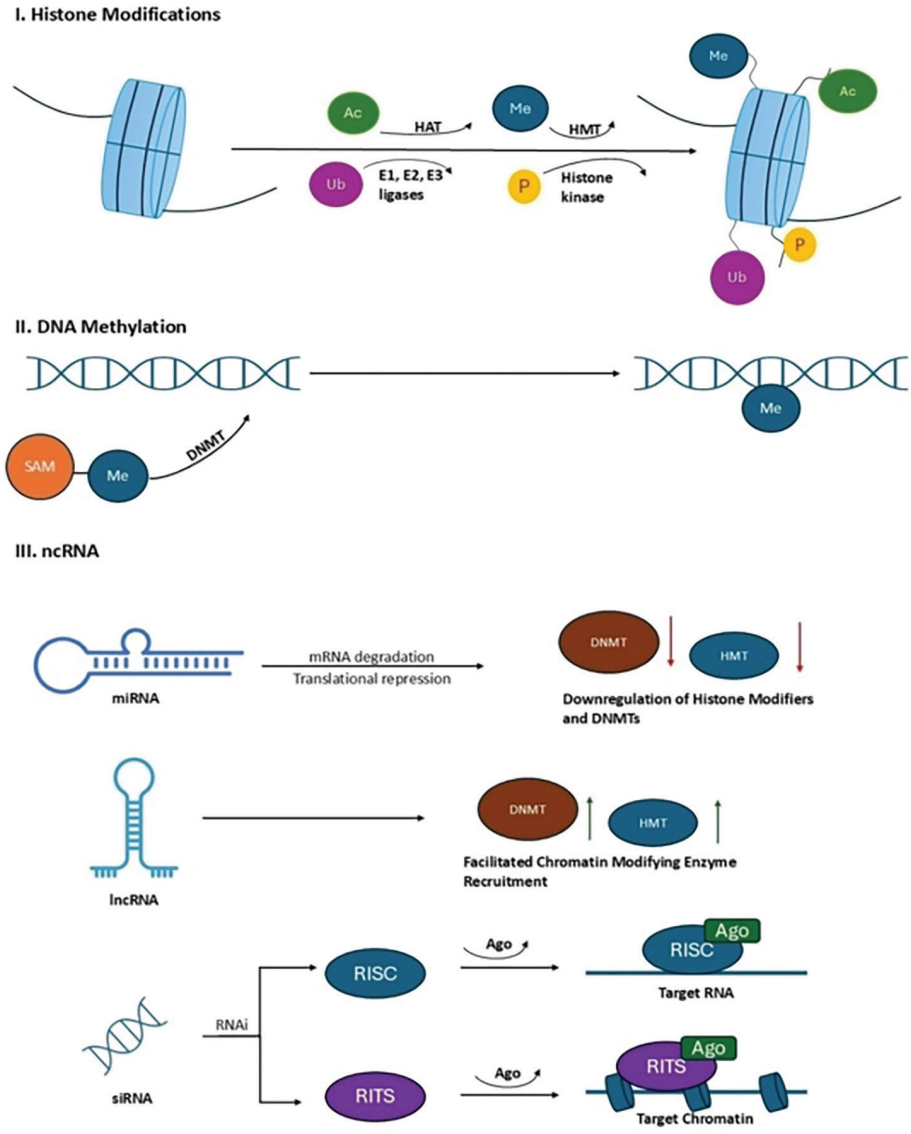

Figure 2: Epigenetic regulation of gene expression. Gene expression is controlled by three key epigenetic mechanisms: Histone modifications-modifications such as histone methylation, acetylation, and phosphorylation alter gene expression by modifying the amino acid residues on histone tails (11, 12-15). DNA methylation-this process involves the transfer of a methyl group from S-adenosyl methionine to the cytosine residue in DNA, leading to transcriptional repression (11, 12). ncRNAs, such as miRNAs, siRNA and lncRNA interact with various factors to regulate transcription (18-25). miRNA downregulates the histone modifying enzyme recruitment by either mRNA degradation, or translational repression (19). This results in altered gene expression. Though the roles and functions of most lncRNAs are yet to be discovered, the prevalent insights regarding lncRNAs indicate that they promote the recruitment of chromatin-modifying enzymes to particular genomic loci, thereby altering the chromatin or DNA state (26). siRNAs function via RNAi mechanisms to inhibit gene expression at either the transcriptional or post-transcriptional stage (24). Ago proteins, in conjunction with siRNA, constitute the central components of RISC and RITS, which are key effectors in the RNAi pathway (24). The interaction between the guide strand and the target RNA through complementary base-pairing facilitates the cleavage of the target RNA (24). This figure was created using the program: Microsoft Powerpoint.

Ac: Acetylation, DNMT: DNA methyltransferase, Me: Methylation, miRNA: microRNA, SAM: S-adenosyl methionine, P: Phosphorylation, Ub: Ubiquitination, HAT: Histone acetyltransferase, HMT: Histone methyltransferase, ncRNA: Non-coding RNA, mRNA: Messenger RNA, siRNA: Small interfering RNA, RNAi: RNA interference, RISC: RNA-induced silencing complex, RITS: RNA-induced transcriptional silencing complex, Ago: Argonaute proteins, lncRNA: Long non-coding RNA, RNAi: RNA interference, DNA: Deoxyribonucleic acid, RNA: Ribonucleic acid

processes, beyond diet and exercise alone, play a significant role in regulating body weight and fat mass (28). One of the physiological processes contributing to the frequency of weight regain is epigenomic alteration, which creates an "obesogenic memory" that diminishes the long-term benefits of calorie restriction (29-31). This obesogenic memory not only promotes a persistent tendency to regain weight but may also underlie the metabolic impairments observed in individuals with obesity (30). Hinte et al. (30) recently demonstrated, through single-nucleus RNA sequencing, that both human and mouse ATs retain cellular transcriptional changes even after significant weight loss. Furthermore, they found that the epigenomes of mouse adipocytes remain persistently altered by obesity, impairing their functionality and responsiveness to metabolic stimuli (30).

While metabolic adaptations in response to weight loss are known to persist long-term, the duration of this persistence varies based on the method by which the weight loss was achieved (29, 30). Bariatric surgery is a common treatment for obesity, particularly in severely obese patients who have not succeeded with non-invasive weight loss methods (32). One of the most recent findings is that, compared with patients who lost weight by calorie restriction, those who underwent bariatric surgery had only a transient decrease in basal metabolic rate (BMR), as opposed to persistently low BMR rates (29, 33). This suggests that bariatric surgery may be more effective than conventional methods in countering treatment against epigenetic obesogenic memory. However, the exact molecular mechanisms underlying this phenomenon remain unknown, making it difficult to overcome this barrier to achieving long-term treatment success (30).

Influence of Epigenetic Alterations in Obesity and Its Comorbidities

Obesity is an increasingly problematic health issue, as the worldwide incidence of obesity has markedly escalated over the last four decades, rising from 3% to 11% among men and from 6% to 15% among women during the same timeframe (34). Type 2 diabetes, cardiovascular disease, and several types of cancer are the primary adverse effects of obesity, which have already contributed to a reduction in average life expectancy (35). The development of obesity-related comorbidities, such as type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease, is influenced by a combination of pathophysiological and environmental factors (36). Given that epigenomic alterations influence various biological systems, it is reasonable to assume that epigenetics also plays a reciprocal role in the development of obesity and its related comorbidities. A study conducted in a young cohort identified multiple CpG sites associated with obesity and found that the variance in DNA methylation was greater in obese individuals compared to lean controls (37, 38). The study also demonstrated that obesity could be predicted with 70% accuracy using both differential methylation and differential variability (37, 38). Another study newly identified 33 CpG sites associated with waist circumference and 70 CpG sites linked to BMI (39). These CpG sites accounted for 25.9% of the variation in waist circumference and 29.2% of the variation in BMI, respectively (39). Another study identified 3529 differentially methylated regions (DMRs) located within or near genes in adipocytes, using a combination of DNA methylation capture sequencing and reduced representation bisulfite sequencing in 11 lean and 12 obese pigs (40). This study also identified 276 differentially expressed transcripts with at least one DMR by sequencing the transcriptome from the same fraction of isolated adipocytes (40). These transcripts were found to be overrepresented in insulin signaling, metabolic, and mitogen-activated protein kinase gene pathways (40).

One of the most common comorbidities of obesity, type 2 diabetes, has also been shown to involve epigenomic changes that contribute to its pathophysiology (38). It was discovered that the islets from type 2 diabetes donors exhibited lower expression of key genes and increased DNA methylation, which were associated with impaired insulin secretion (38). Additionally, elevated hemoglobin A1c and glucose levels appeared to directly increase DNA methylation of these genes (38). Nilsson et al. (41) demonstrated that in the livers of type 2 diabetes patients, individuals with the condition showed reduced DNA methylation at 94% of the significant CpG sites. The observed hypomethylation in the livers of diabetic subjects could be attributed to reduced folate levels (41). Indeed, those with type 2 diabetes had significantly lower erythrocyte folate levels compared to individuals without diabetes (41). Even more interestingly, another study found that women with higher folate intake had a lower risk of developing diabetes (38, 42). This suggests that epigenetic changes influenced by folate intake might play a role in the development of diabetes. However, genetic studies indicate that the effect size of each CpG site is relatively small (38). This is not surprising, as type 2 diabetes is a complex, multifactorial, and polygenic disease, making it unlikely that methylation of a small number of CpG sites would have a significant impact on the disease (38).

Epigenetics and Susceptibility to Obesity

Studies indicate that individuals with a genetic predisposition for AT accumulation are also more susceptible to adverse environmental factors, which renders them more prone to weight gain (43). This phenomenon is known as gene-by-environment interaction, and it is mediated through epigenetic mechanisms (43). Viable yellow (Avy) mutation in the agouti mouse model illustrates how epigenetics influence obesity (43, 44). For context, it is worth mentioning that Avy mutation is one of two dominant mutations of the *Agouti* gene on mouse chromosome 2 (45). This mutation manifests a phenotype characterized by yellow fur, significant obesity, insulin resistance, and vulnerability to tumorigenesis (45). When these mice are fed a diet high in methyl donors, the mutation that disrupts melanocortin-4 receptor and causes obesity can be reversed (43, 44). This demonstrates a connection between

environmental-driven epigenetic changes and obesity (43, 44). Another study discovered that in obese subjects, weight was inversely correlated with the rate of DNA methylation at the leptin gene's promoter region (46). Additionally, the study's results indicated a negative correlation between DNA methylation levels and total cholesterol, insulin resistance (measured by the homeostatic model assessment), glucose, and fasting insulin (46). Compared to non-obese subjects, obese individuals also exhibited higher expression of DNMT1 and DNMT3b (46). This finding suggests that the epigenomic profile of leptin is likely associated with obesity and its risk factors, thereby increasing the likelihood of comorbidities (46).

There is limited research supporting transgenerational epigenetic inheritance in humans, and the dynamic, transient nature of epigenetic modifications presents additional challenges in this area of study (38). Outside of human research, actual transgenerational epigenetic effects are still poorly understood, with most observations being made in Caenorhabditis elegans (38). However, several studies have attempted to investigate the transmission of epigenetic mechanisms across generations and their relationship to type 2 diabetes and obesity (38). The rapid rise in the prevalence of metabolic and chronic diseases may partly explained by the fact that obese mothers can pass on their metabolic phenotypes to their children, increasing the risk of chronic metabolic diseases (8). One proposed mechanism for this is epigenetic inheritance.

Epigenetics in Central Nervous System (CNS) Regulation of Appetite and Metabolic Pathways

It is well-established that the CNS has a major influence on other organs and systems (47-49). Given this, it is reasonable to suggest that the CNS also plays a critical role in the gastrointestinal and endocrine systems (48, 50, 51). One of the mechanisms through which the CNS may exert its influence is

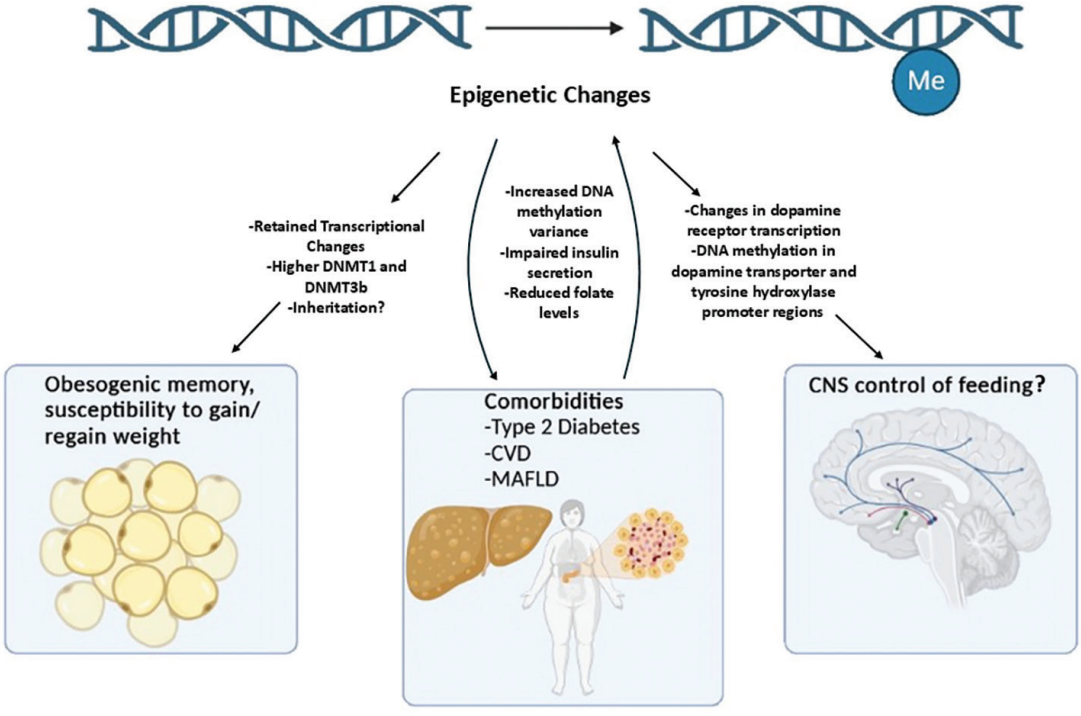

Figure 3: Epigenetics and White Adipose Tissue. Epigenetic changes play a significant role in both weight gain and weight maintenance, influencing the development and persistence of obesity (8, 29-31, 43, 50). It was recently demonstrated that both human and mouse ATs retain cellular transcriptional changes even after significant weight loss (30). Furthermore, the epigenomes of mouse adipocytes remain persistently altered by obesity, impairing their functionality and responsiveness to metabolic stimuli (30). Studies indicate that individuals with a genetic predisposition for AT accumulation are also more susceptible to adverse environmental factors, which renders them more prone to weight gain (43). This phenomenon is known as gene-by-environment interaction, and it is mediated through epigenetic mechanisms (43). Epigenetic changes also exhibit a reciprocal relationship with obesity-related comorbidities. Multiple CpG sites associated with obesity were identified and found that the variance in DNA methylation was greater in obese individuals compared to lean controls (37, 38). It was also observed that the islets from type 2 diabetes donors exhibited lower expression of key genes and increased DNA methylation, which were associated with impaired insulin secretion (38). People with type 2 diabetes had significantly lower erythrocyte folate levels compared to individuals without diabetes (41). Additionally, in a study, women with higher folate intake had a lower risk of developing diabetes (38, 42). This suggests that epigenetic changes influenced by folate intake might play a role in the development of diabetes. Epigenetic modifications may have the potential to regulate appetite through transcriptional changes in the CNS. It has been observed that rodents chronically fed a high-fat diet show significant changes in dopamine receptor transcription (50). More notably, differential DNA methylation was found in the dopamine transporter and tyrosine hydroxylase promoter regions, and the pattern of this methylation response corresponded with changes in gene expression (50). This figure was created using the programs: BioRender and Microsoft Powerpoint.

CNS: Central nervous system, CVD: Cardiovascular diseases, MAFLD: Metabolic-associated fatty liver disease, Me: Methylation, AT: Adipose tissue, DNA: Deoxyribonucleic acid, WAT: White adipose tissue, DNMT: Deoxyribonucleic acid methyltransferase

through epigenetic changes. This idea is further supported by Gupta-Agarwal et al. (52), who identified 507 epigenetically related genes in the hippocampal cornu ammonis (CA1 region of the hippocampus). Given the CNSs important role in the hedonic control of appetite, it is reasonable to question whether epigenetics also plays a role in appetite regulation. Studies suggest that this may indeed be the case. It has been observed that rodents chronically fed a high-fat diet show significant changes in dopamine receptor transcription (50). More notably, differential DNA methylation was found in the dopamine transporter and tyrosine hydroxylase promoter regions, and the pattern of this methylation response corresponded with changes in gene expression (50). This suggests that the reward circuitry involved in the hedonic regulation of feeding may be influenced by epigenetic changes. However, much remains unknown about the functional role of these epigenetic modifications in the CNSs control over energy and glucose metabolism (29).

Epigenetics and Brown Adipose Tissue

As mentioned previously, recent studies suggest the existence of at least two types of thermogenic AT: pre-existing BAT and inducible BeAT (1, 7, 8). Classical BAT originates prenatally from a specific group of dermomyotome cells and is mainly found in specialized BAT locations, which typically diminish in adult humans (7). In contrast, BeAT, also referred to as "inducible BAT", is believed to originate from WAT and is induced under conditions such as cold exposure and exercise (7). Although it is known that BeAT is derived from WAT, the precise origin of this tissue remains unclear. However, it seems likely that epigenetic modifications play a significant role in the development of these cells.

Recent studies have identified approximately 50 transcriptional and epigenetic regulators that either promote or inhibit the development of BAT and BeAT (53). Notably, nearly all of these regulators function through four key transcriptional factors: *peroxisome proliferator-activated receptor γ*, *CCAAT-enhancer-binding protein*, *PPARγ co-activator-1α*, and *PR domain containing 16* genes (Figure 4) (53). Some of these epigenetic factors include several miRNAs, dimethyltransferases such as euchromatic histone lysine methyltransferase 1 and euchromatic histone lysine methyltransferase 2, and a lncRNA called Brown fat lncRNA 1 (53).

CONCLUSION

Adipose tissue plays several critical roles beyond fat storage and lipid regulation in the body's physiological and pathological functions, including thermogenesis and hormone regulation. These functions are governed by various mechanisms, one of which, epigenomic modifications, has gained recent attention. Studies on BeAT/BAT and WAT highlight the significant role of epigenetics. While epigenetics may also influence pink AT, there

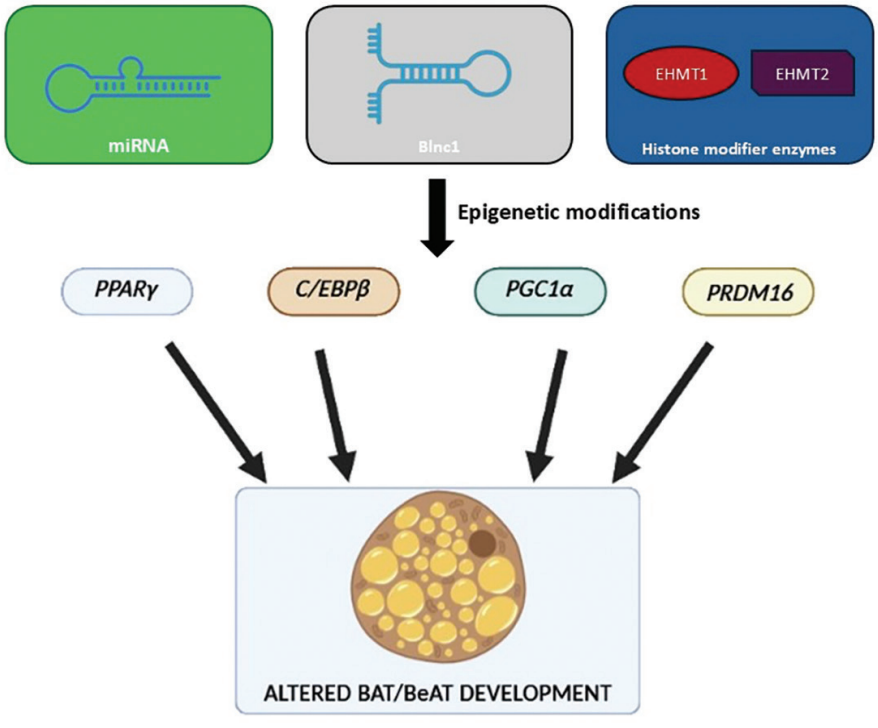

Figure 4: Epigenetic regulation of BAT/BeAT development. Nearly all epigenetic modifications involved in the development of BAT and BeAT function through the *PPARγ*, *C/EBPβ*, *PGC1α*, and *PRDM16* genes (53). Some of these epigenetic factors include several miRNAs, dimethyltransferases such as EHMT1 and EHMT2, and a long non-coding RNA called Blnc1 (53). This figure was created using the programs: BioRender and Microsoft PowerPoint.

BAT: Brown adipose tissue, BeAT: Beige adipose tissue, C/EBPβ: CCAAT-enhancer-binding protein, PGC1α: PPARγ co-activator-1α, miRNA: micro ribonucleic acid, Blnc1: Brown fat lncRNA-1, EHMT: Euchromatic histone-lysine N-methyltransferase

is still limited research in this area, making it unclear. However, when it comes to pathological conditions like obesity and its comorbidities, there is a wealth of evidence to explore. Several studies suggest that epigenetic mechanisms may contribute to the development and maintenance of obesity through various pathways, such as creating an obesogenic memory, increasing susceptibility to environmental factors that promote weight gain, affecting the central CNS and indirectly controlling appetite, and possibly through epigenetic inheritance. Since epigenetic changes are reversible, there is hope for therapeutic interventions that target these changes, offering potential treatments for major diseases such as obesity and type 2 diabetes.

Ethics

Ethics Committee Approval: *N/A.*

Informed Consent: *N/A.*

Footnotes

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Concept: A.U., Design: A.U., S.E., Analysis and/or Interpretation: A.U., Literature Search: A.U., Writing: A.U., S.E.*

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