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Research on the Relationship between Obesity and Epigenetics and its Application

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Abstract. Obesity is a complex and persistent disease that has been considered an epidemic with serious implications for public health and the global economy, given the rapid increase in its prevalence across all age groups. Pathogenesis of obesity involves environmental and genetic factors. Environmental factors are essential in modifying the epigenome, which in turn affects gene expression and contributes to obesity. This article provides a concise overview of the current knowledge about the connection between epigenetics and obesity, with a specific emphasis on DNA methylation, histone modifications, and non-coding RNAs. The study also investigates two primary mechanisms of epigenetic transgenerational inheritance, which refers to the phenomenon where environmental damages encountered by one generation can impact the susceptibility to obesity in future generations. The article aims to highlight the importance of epigenetics in obesity development and to propose potential interventions for its prevention and treatment.

Keywords: Obesity, Epigenetics, DNA methylation, Histone modifications, Non-coding RNAs, Transgenerational inheritance, Environmental factors, Epigenetic therapies.

1. Introduction

A chronic and complicated illness, obesity is defined as too much fat accumulating in the body compromising health. Obese people have a body mass index (BMI) of 30 kg/m² or more [1]. Obesity is fast rising in frequency throughout the world. From 1990 to 2022, the percentage of people aged 5–19 with obesity increased fourfold, rising from 2% to 8%, while that of adults aged 18 and older with obesity more than doubled, growing from 7% to 16% [2]. Frequently, obesity is linked to the development of other pathologies, such as cardiovascular diseases and type 2 diabetes mellitus [3]. In 2019, elevated BMI caused nearly 5 million deaths. If sufficient measures are not implemented to mitigate the obesity epidemic's progression, the annual global economic burden is projected to escalate to $3 trillion by 2030 [4, 5]. Given the threats posed to public health and the economy, there is a strong need to understand its etiology to develop effective therapeutics.

Many factors contribute to obesity, including genetic mutations and environmental insults. [6]. Mutations in genes related to monogenic obesity, such as the leptin receptor (LEPR), are known to lead to early onset obesity [7]. However, through genome-wide association studies (GWAS), it was discovered that the susceptibility variations found account for only a small portion of the individual variation in the risk of obesity [8]. Additionally, given that genomes cannot undergo major alterations

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in a few years, the fast rise in the frequency of obesity makes theories based purely on genetic changes improbable [9].

Environmental factors can potentially change the epigenome, alter gene expression, and lead to obesity [10]. Small sample sizes and focus on several targeted CpG sites limited early studies on epigenetics. Lately, advances in technologies have enabled researchers to focus on complex interactions between environmental factors, epigenome, and phenotypes. This article provides a concise overview of the current state of knowledge regarding the correlation between obesity and epigenetics. The article reviews the correlations between obesity development and DNA methylation, histone modifications, and non-coding RNAs. Additionally, it discusses the transgenerational inheritance of epigenetic information and its impact on obesity. This review intends to support efforts to create new obesity treatments and prevention measures.

2. Epigenetics and obesity

Compared to genetic mutations, which involve variations in the DNA base sequence, epigenetic changes are typically reversible and involve chemical modifications to DNA or histone proteins without altering the DNA sequence. Epigenetic marks are inheritable, and they can influence gene transcription through various processes, most notably the addition of methyl groups to DNA (DNA methylation), posttranslational modifications to histone, and the action of non-coding RNAs. These processes alter the accessibility of the transcriptional machinery to specific genes, thereby regulating gene transcription [11].

2.1. DNA methylation

In mammalian genomes, methylation predominantly occurs at CpG sites. DNA methylation is able to regulate gene expression by inhibiting the binding of transcriptional factors to DNA or recruiting proteins that are involved in gene repression [12]. The change in global methylation patterns is recognized as a hallmark of cancers. However, this phenomenon is not considered to be associated with obesity as it's more subtle and thus harder to detect, given the influence of many other factors on global methylation patterns [9]. Methylation analysis of specific genes gives a better picture of their associations with obesity. The analysis centers on genes implicated in obesity, growth, appetite, circadian clock control, weight loss regain, and insulin signaling. Changes in the methylation levels of specific genes were observed when obesity was diagnosed. Decreased methylation was noticed in leptin (LEP) in whole blood (WB) [13], tumour necrosis factor alpha (TNFα) in peripheral blood leukocytes (PBL) [14], pyruvate dehydrogenase kinase 4 (PDK4) in muscle tissues [10], etc. Increased methylation was noticed in proopiomelanocortin (POMC) in WB, members in insulin signalling pathways, such as insulin (INS), and PPARγ coactivator 1 alpha (PGC1α) in muscle, etc [10, 15, 16]. These findings prove that obesity is closely related to methylation states of metabolically crucial genes and offer new avenues for diagnostic or therapeutic purposes, given that methylation is a reversible chemical modification whose level is measurable.

2.2. Histone modifications

Histone proteins are located in the cell nuclei, facilitating the compaction of DNA into nucleosomes, which are further wrapped into 30-nanometer fibers that form highly compact chromatin structures [17]. Histone modifications, such as acetylation, methylation, and phosphorylation, usually occur at the N-terminal of histone proteins, and they regulate the gene expression also by controlling the accessibility of transcriptional factors to DNA. For example, acetylation neutralizes the positively charged lysine residues from histone tails. This makes the DNA less dense and more open to transcriptional factors (weaker electrostatic interactions). Acetylation can also facilitate the recruitment of bromodomain proteins, which are involved in remodelling chromatin and recruiting other transcriptional factors [18]. Histone modifications regulate the transcription of five crucial adipogenesis genes and can influence the development of obesity. They are CCAAT-enhancer-binding protein β (C/EBPβ), C/EBPα, preadipocyte factor-1 (Pref-1), adipocyte protein 2 (aP2), and PPARγ [19]. Histone modifications also

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engage in the controlling of the expression of appetite-control genes. Specifically, increased H3K9 acetylation was found to be related to Neuropeptide Y (Npy), while decreased acetylation on the same residue was associated with Proopiomelanocortin (Pomc) [20]. Obesity closely correlates with the levels of enzymes responsible for histone modifications, including histone deacetylases (HDACs), histone acetyltransferases, histone demethylases, and histone methyltransferases. In response to fasting and meals high in fat, the medial hypothalamus alters the expression of neuropeptides engaged in the regulation of HDACs, which can modify histones and regulate gene expression. A study on mice found that after feeding them fat-rich diets for four weeks, there were increased levels of HDAC5 and HDAC8. On the other hand, fasting subjects showed increased levels of HDAC3 and HDAC4, but decreased levels of HDAC10 and HDAC11 [21].

2.3. Non-coding RNAs

Non-coding RNAs (ncRNAs) are functional RNA molecules that are not translated into proteins. NcRNAs have the ability to regulate gene expression at the RNA level. For instance, microRNAs (miRNAs) are short ncRNAs that repress genes by attaching to coding and untranslated regions of targeted messenger RNAs (mRNAs). This binding can result in either the deterioration of the mRNA or the inhibition of its translation into protein, thereby reducing the expression of that gene [22]. Additionally, miRNAs can control chromatin remodeling and DNA methylation as chromatin domain proteins, HDACs, methyl CpG binding proteins, and histone methyltransferases are all potential targets for miRNAs. miRNAs perform a significant role in adipocyte differentiation and obesity growth. Specific miRNAs have been found to be expressed in mice that have been fed with fat-rich diets. The changes in their levels during the development of obesity were also noticed. miR-192, miR-30a, miR-1, miR-133b, miR-122 and miR-203 were down-regulated, while miR-142-3p, miR-342-3p, miR-146a, miR-21, miR-142-5p, miR-146b, and miR-379 were up-regulated [23]. In other studies, researchers have found that miR21 and miR221 were more abundant in the white fat tissue of obese people. miR221 level was also elevated in mice that were obese due to fat-rich diets. When experimentally reduced these miRNAs, triglyceride storage decreased, and the process of creating new fat cells (adipogenesis) was reduced. Additionally, lower BMIs were observed, indicating fat reduction. Numerous additional miRNAs have also been shown to be expressed differently in obese people. These miRNAs are involved in important processes such as insulin signalling, hypoxia response (which adapts to decreased oxygen levels and affects various metabolic pathways), and adipogenesis [24]. Long non-coding RNAs (lncRNAs), another type of ncRNA that are longer than 200 nucleotides, are also important in adipose tissue function. A study aimed at investigating if lncRNAs play a role in childhood obesity has found that there are 1268 lncRNAs that are produced differently in overweight and normal-weight children. lncRNAs RP11-20G13.3 and GYG2P1 were identified to be strongly associated with pathogenic mechanisms of childhood obesity as they have a strong correlation with clinical features like BMI-SDS, waist-hip ratio, waist circumference, fasting insulin, LDL cholesterol, hsCRP and leptin [25].

3. Epigenetic transmission of obesity susceptibility across generations

Exposure of ancestral germline cells to toxins in the environment and adjusting their diet can change their epigenome. Through a process of transgenerational inheritance based on epigenetic modifications, this reprogramming can pass on the vulnerability to obesity to subsequent generations. Environmental insults like maternal malnutrition, alcohol intake, sleep disturbance, high-fat diets, use of epigenetic drugs, hypoxia, and exposure to endocrine-disrupting chemicals can play a crucial role in the development of adipose tissue and childhood obesity.

3.1. Epigenetic developmental reprogramming

The epigenome of a cell can contribute to mitotic memory as it is responsible for maintaining stable gene expression patterns in particular cell types to preserve lineage fidelity and cell identity. However, shortly after fertilization and during the development of primordial germ cells (PDCs), the epigenome is reprogrammed to convert differentiated cells to totipotent or pluripotent cells, which are critical for

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further embryogenesis and fetal development [26]. During these critical reprogramming phases, environmental influences, such as different toxicants have the potential to permanently alter the epigenetic information of the fetal and subsequent somatic cells [27].

3.2. Mechanisms

Epigenetic transgenerational inheritance occurs when the germline transmits epigenetic information across successive generations. This leads to phenotypic differences that the environment does not directly cause. The inheritance process primarily involves two mechanisms. The first one is that during the gestational period, the environmental insults experienced by a gestating female (F0) can result in epigenetic changes, such as methylation pattern alteration in the fetus (F1). In addition, these changes in the germline cells (F1) will further influence the next generation (F2). F2 generation is therefore still considered to be directly exposed to the environmental factors. Epimutation can be considered transgenerationally inheritable only if the modified epigenome is transmitted to the F3 generation[28]. The second mechanism is that the preconception exposure of male or female(F0) to the environmental insults can directly affect their germline cells, which eventually become the F1 generation. Therefore, this mechanism allows environmental insults to directly influence the F1 generation. An epimutation is considered transgenerationally inherited if the epigenome of the F2 generation is altered [28].

Changes in the epigenome of germline cells can potentially impact the epigenome of totipotent cells during the initial phases of embryonic development, regardless of the mechanisms. Afterward, these stem cells can induce epimutations in various somatic cell types that they develop into. Therefore, a cascade of epigenome and genetic expression changes is generated along with cellular differentiation. As anticipated, the organism's transcriptome and physiology are more significantly affected by exposure to environmental insults during the early crucial windows than by exposures occurring later in development. In general, alterations in the epigenetic state induced by the environment can influence the functioning of the genome and the transcriptome unique to cell types, rendering individuals more prone to disorders such as obesity[29].

4. Discussion

Considering the reversible and modifiable nature of epigenetic modifications, there are some therapeutic strategies that could be applied to prevent obesity, especially during the early development stage, where exposures to environmental insults have the largest impact. Specifically, it could be achieved by adopting healthy diet habits before and during these early critical windows of development [30]. The period for implementing this strategy is longer than initially expected. Rather than being effective only during pregnancy, neonatal, and infant stages, this strategy remains effective for nearly 1000 days after conception [31]. Instead of relying on epigenetic drugs, which are still in the early stages of development, adopting dietary changes is currently the safest, most affordable, and widely accepted approach.

Human milk contains abundant amounts of miRNAs that can induce epigenetic modifications, such as miR-21 and miR-152, targeting DNA methyltransferases. Based on this, researchers have hypothesized that the epigenetic information could be directly transferred via the breast milk [32]. Studies have shown that maintaining a typical pre-pregnancy body mass index and long-term exclusive breastfeeding provide advantages. These elements not only immediately support weight control but also assist with preventing later in life the development of nonalcoholic fatty liver disorder [31]. While these strategies are safe and affordable, their effectiveness can be limited by conditions such as hypogalactia, which is insufficient milk production caused by factors like hormonal imbalances, stress, and nutritional deficiencies.

Pharmacological interventions could also be a promising approach. Supplementing the maternal diet with methyl donors during breastfeeding inhibits the occurrence of fatty liver and obesity traits in mice pups [33]. It is also found that the control of hunger and metabolism in humans can be done by supplementing both paternal and maternal diets with molecules that can change the methylation states, such as choline, folate, and methionine [34, 35]. However, more research is needed to reveal the

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correlation between parental involvement of methyl donors, methylation levels of specific DNA, and subsequent outcomes as it is less direct than expected.

5. Conclusions

Over the past 30 years, there has been a sharp rise in the prevalence of obesity, making it a global health concern. Considering the significant threats to public health and the economy posed by obesity and its comorbidities, the attention on addressing obesity has reached an unprecedented level. A review of previous research reveals that complex interactions among genetic, environmental, and developmental factors influence obesity. The relationship between obesity and epigenetics offers new avenues for potential treatment strategies. Researchers have made initial progress in finding putative obesity biomarkers that are detectable when born. This advancement might eventually enable the prediction of an individual's early-life obesity risk, prior to phenotype's manifestation, thereby facilitating the introduction of targeted preventative strategies.

Because epigenetic alterations are reversible, they present a viable target for prospective obesity-related epigenetic therapeutics. Keeping the mother's body mass index (BMI) in a healthy range, breastfeeding exclusively, and adding epigenetic modifiers to the mother's diet during key developmental windows have all been shown to be effective in animal models and should be investigated further in humans. Increasing evidence supports the use of epigenetic drugs, which are compounds capable of modulating epigenetic mechanisms, in the treatment of obesity. However, further investigation is necessary to comprehend the connection between types and dosages of ingested epigenetic modifiers, how the epigenome of targeted genes changes, and subsequent phenotypic outcomes, due to the complexity of these interactions.

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