American Journal of
Biomedical Science & Research

www.biomedgrid.com
ISSN: 2642-1747

Mini Review

Transgenerational Transmission of Epigenetic Modifications in Development of Obesity and Other Chronic Diseases

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To Cite This Article: *Yi Li. Transgenerational Transmission of Epigenetic Modifications in Development of Obesity and Other Chronic Diseases. Am J Biomed Sci & Res. 2022 - 16(4). AJBSR.MS.ID.002257.* DOI: 10.34297/AJBSR.2022.16.002257

Received: June 13, 2022; **Published:** June 22, 2022

Abstract

Obesity is a chronic condition that is also a risk factor of several other chronic conditions including type 2 diabetes, cardiovascular disease, hypertension, cancer, and neurodegeneration diseases. Chronic conditions are caused by environmental factors including dietary and lifestyle factors and are developed over long periods of time. Mechanism studies indicate that epigenetic modifications induced by environmental factors are involved in development of chronic conditions. One of the important questions in the area of obesity and other chronic diseases study is to address the mechanisms that how parental chronic diseases affect the health of the offspring. In addition to the possible permanent changes of the organs caused by the intrauterine environment hypothesized by the Developmental Origins of Health and Disease (DOHaD) theory, recent evidence indicates that the effects of parental obesity and chronic diseases on fetal development and offspring health are mediated through the transmission of epigenetic modifications via both the female germline and the male germline. Obesity and type 2 diabetes are closely related with each other. Along with the mechanism studies using animal models, the current priorities in obesity and type 2 diabetes research are identification and confirmation of the specific epigenetic biomarkers associated with obesity and type 2 diabetes in human subjects and identification of the dietary and lifestyle factors that contribute to each of the identified specific epigenetic biomarkers.

Introduction

The prevalence of obesity and type 2 diabetes have dramatically increased in recent decades in the US and worldwide [1]. Obesity is also a risk factor of other chronic conditions including cardiovascular disease, hypertension, and cancer, etc. [2, 3]. Chronic conditions including cardiovascular disease have been ranked as the top causes of death in recent years. Obesity is defined by increased body weight as a result of accumulation of extra energy as lipids in the adipose tissue of the body. Obesity is associated with insulin resistance and low-grade inflammation [4]. Type 2 diabetes is characterized as insulin resistance associated with dysregulation of blood glucose homeostasis [5]. There are more than 90% of the type 2 diabetes patients developed from obesity [5]. Therefore, obesity and type 2 diabetes are closely related chronic conditions with some shared common characteristics including higher blood glucose levels caused by insulin resistance. As chronic conditions closely related with dietary and lifestyle factors, these factors are involved in development of obesity and type 2 diabetes. On another hand, children of the mothers with diabetes have increased risk to become obese [6]. The etiology studies reveal that obesity and type 2 diabetes are caused by genetic and environmental factors including dietary and lifestyle factors [7]. However, the pathologic mechanisms involved in development of obesity and type 2 diabetes are still not totally clear.

Parental Effects on Development of Obesity

It has been speculated by the Developmental Origins of Health and Disease (DOHaD) hypothesis that the fetal and infant phases of life have effects on development of adult obesity and metabolic disorders [8]. The fetus makes predictive adaptations in response to the factors in the intrauterine environment, resulting in permanent adjustments in organs involved in the homeostatic regulations to adapt the intrauterine and possible adverse postnatal environment [9]. These permanent changes of certain organs at specific developmental stages of the fetus caused by the intrauterine environment factors may have adverse long-term health effects on the adult offspring. This hypothesis can be perfectly used to explain that the children born to the mother exposed to famine during the pregnancy had increased adiposity and metabolic disorders [9]. However, organisms survive by adapting the constantly changing environment over the time not only at one time point.

Recent studies indicate that epigenetic modifications altered by environmental factors including dietary and lifestyle factors are involved in development of obesity and type 2 diabetes in addition to the involvement of genetic factors such as Single Nucleotide Polymorphisms (SNPs) [10-12]. Epigenetic modifications, the modifications on top of the genetic coding, are the modifications added to the genome rather than changing of the genetic coding. These epigenetic modifications typically include genomic DNA methylation, histone tail modifications, and Non-Coding Small RNAs (ncRNAs) such as microRNAs (miRNAs) [7]. It has been demonstrated that these epigenetic modifications can affect each other. For example, methyl CpG-binding protein 2 binds to methylated DNA and subsequently recruits enzymes such as histone deacetylases and histone demethylases to modify histones [13,14]. Environmental factors including dietary and lifestyle factors induce changed levels of epigenetic modifications and subsequently cause change of expression of genes involved in development of chronic diseases [7-15]. In real life, it takes long periods of time for the environmental factors to cause changes of epigenetic modifications involved in development of chronic conditions. That is why chronic conditions such as obesity, type 2 diabetes, and cardiovascular disease may take years and decades to develop.

Transgenerational Transmission of Epigenetic Modifications

The statistical data indicate that increasing prevalence of childhood obesity is well correlated with increasing adulthood obesity and type 2 diabetes [1-16]. Human obesity and diabetes are associated with reproductive disorders including low fertility [17]. It is interesting to notice that the maternal effects are considered in most of the human studies addressing childhood obesity while the sperms from the paternal side are being paid more attention when addressing reproductive issues of parents with obesity and other chronic conditions [16,17]. In addition, it has been demonstrated using rodent models that both maternal oocytes and paternal sperms with altered epigenetic modifications from obese parents are involved in adversely affecting health of the offspring [18-20]. When a recent study using mouse model to study the parent-of- origin effects of obesity, an increased obesity incidence in the F4 generation maternal outcross male offspring was observed, indicating the obesity transmission was mainly passed via the female germline allele to the male offspring, while an increased obesity incidence in the F4 generation paternal outcross female offspring was observed, indicating the obesity transmission was mainly passed via the male germline allele to the female offspring [21]. These lines of evidence suggest that altered epigenetic modifications of gametes from obese parents are involved in passing on obesity to the offspring. The detailed mechanisms of transgenerational transmission of epigenetic modifications associated with chronic conditions are currently being studied further [22].

Research on transgenerational transmission indicates the obese male individuals affect the health of the offspring through the epigenetic modifications carried by the sperm, including altered levels of global DNA methylation, histone acetylation, and ncRNA [20-24]. Male obesity model induced by high-fat diet affect the metabolism and reproduction of the F1 generation associated with reduced sperm motility and increased DNA damage [25]. High-fat diet reduces global genomic DNA methylation levels in the sperm and in the spermatozoa of the offspring [26,27]. Increased H3K9 acetylation associated with decreased sirtuin 6 (SIRT6) deacetylases in the nucleus of male mouse sperm caused by high-fat diet is associated with increased DNA damage [28]. These results are further confirmed by that increased overall histone acetylation levels during sperm maturation caused by inhibition of histone deacetylase by Trichostatin A are associated with decreased sperm quantity and DNA damage [29, 30].

When high fat diet induced obesity mouse model was used to study the alteration of the sperm miRNA levels, differential expression of miRNAs was observed in the sperms of the obese mice induced by high fat diet, however the same set of the abundant miRNAs were not observed in the sperms of the F1 offspring male mice even the metabolic and reproductive phenotypes were also observed on the F2 offspring mice [24]. This probably means that there are other epigenetic modifications associated with the phenotypes involved in transgenerational transmission of obesity to the F2 offspring mice. This might also suggest that there are other mechanisms in addition to epigenetics involved in transgenerational

transmission of obesity. DOHaD hypothesis might be one of the possible mechanisms. The effects of maternal obesity and type 2 diabetes on fetal development and offspring health are mediated through the epigenetic modifications transmitted from the mother to the offspring in addition to the possible permanent changes of the organs caused by the intrauterine environment hypothesized by the DOHaD theory [31]. Increased overall DNA methylation levels are observed in oocytes of mice of both high-fat diet and ob/ob obese mouse models with increased methylation levels of the Leptin gene promoter and decreased methylation of the promoter of PPARα gene that encodes for a transcription factor mediating adipogenesis [18,32]. In the adipose tissues of diet induced obese mice, DNA methylation levels of the Leptin gene promoter and the binding of DNA Methyltransferases (DNMTs) are increased [33]. Differential methylation patterns are observed in oocytes of type 1 diabetes mouse model and bovine blastocytes under in vitro hyperinsulinemia [34,35]. Maternal diabetes of mouse models affects methylation levels of imprinted genes in oocytes associated with decreased expression of DNMTs [17].

Perspectives

As epigenetic modifications can be altered by environmental factors including dietary and lifestyle factors, the mechanisms remain unclear how early life malnutrition including energy imbalance can have long-term effects such as obesity and metabolic disorders on the adult offspring. It is likely that epigenetic modifications from the gametes and the permanent adjustments in fetal organs resulted from the intrauterine environment factors are both involved in affecting health of the offspring. As epigenetic modifications such as DNA methylation affecting genetic alterations, the environment is also shaping species through epigenetic modifications during the selection process [36]. Since obesity is the chronic condition that is mostly related with dietary and lifestyle factors as the typical environmental factors, it is expected that many of the remaining questions related with the role of epigenetic modifications in development of chronic diseases will be first addressed in obesity and type 2 diabetes.

The knowledge of epigenetics in obesity and type 2 diabetes will accelerate the studies to address involvement of epigenetic modifications caused by environmental factors in development of other chronic conditions. In obesity and type 2 diabetes research, it is a priority at this time to identify and confirm the specific epigenetic biomarkers associated with obesity and type 2 diabetes in human subjects while the animal models are used to further study the mechanisms of transgenerational transmission of the epigenetic modifications [22]. These biomarkers can be used to develop prognosis strategies. Another priority is to identify the dietary and lifestyle factors that contribute to each of the identified specific epigenetic biomarkers. This knowledge will facilitate developing management strategies for prevention and treatments. Some of the miRNA epigenetic biomarkers associated with obesity and type 2 diabetes may be used directly to develop drugs. For example, if a specific miRNA is identified to inhibit adipogenesis or to facilitate changing white adipocytes to become brown adipocytes, then this miRNA can be synthesized and delivered into white adipose tissues to treat obesity.

Funding

This work was supported by startup funds from Saint Louis University to YL and by the Washington University Institute of Clinical and Translational Sciences which is, in part, supported by the NIH/National Center for Advancing Translational Sciences (NCATS), CTSA grant #UL1TR002345.

Conflicts of Interest

The author declares no potential conflicts of interest.

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