Epigenetics Misregulation and Obesity or Epigenetics: Another Important Piece in the Obesity Puzzle

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In 2016, the World Health Organization (WHO) estimated that 1.9 billion individuals over the age of 18 are overweight which comprises roughly one-third of the world population. Obesity is defined by the presence of abnormal or excessive fat which presents excessive risks to an individual's health. Consequently, obesity is a risk factor for diseases such as cardiovascular disease, diabetes, and cancer. Health care professionals and world organization bodies, such as the WHO, highlight that obesity is preventable. As such, there has been significant research conducted to understand the causes of the pandemic.

The food consumed, in particular, the high calorie-containing diets, is often cited as one of the major factors behind the increased incidence of obesity. The lack of balance between the food consumed and energy expenditure has superimposed resulting in the global pandemic observed.

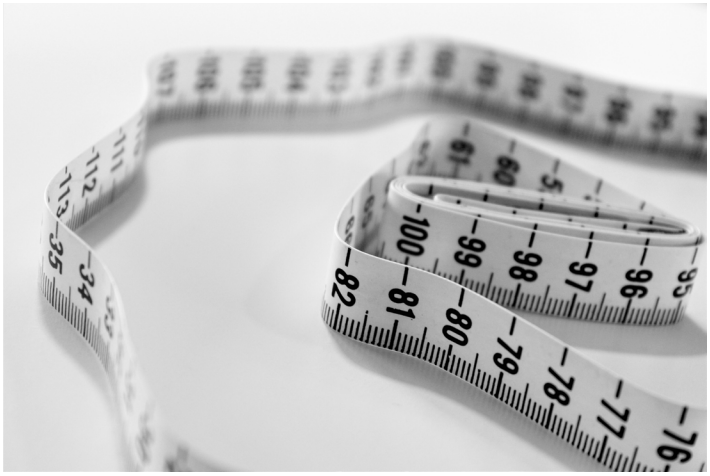
However, diet is not the only factor involved. Over the years, multiple genetic studies, such as monogenic twin studies, adoption studies, in addition to basic science research with animal models has elucidated causative genes which, when mutated, have been shown to cause early-onset obesity. These genes, such as *leptin, leptin receptor,* and *brain-derived neurotrophic factor* to mention a few, are known to regulate metabolic processes and thus, are expected to play a role in obesity.

Questions remained regarding the quantifiable impact of genetic factors and diet contributes on obesity. Currently identified genes explain roughly ten-percent of the risk of obesity and although the role of the environment is slightly higher, the missing heritability of obesity suggests that much of the factors and influences that explain obesity can not be elucidated solely through genetics and diet.

In recent years, epigenetic studies have offered insight into mechanistic molecular explanations that have greatly increased our understanding of obesity. Epigenetics is defined that heritable changes in genetic variation that are not explained by changes to the genetic material itself. Epigenetic mechanisms include changes to DNA methylation, histone modification and non-coding RNA (ncRNA) each of which has been shown to be involved in obesity.

DNA Methylation

DNA methylation is one of the many means through which gene expression can be regulated. Gene expression refers to the activity of a gene. When activated, genes produce



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RNA, a process known as transcription, which eventually produces proteins that carry out downstream functions. However, gene expression is similar to a dial in-which gene can be expressed to a wide range of levels. Some genes are expressed very highly while others at very low levels. DNA methylation plays a role in gene expression because when DNA is methylated, the machinery responsible for initiating gene expression cannot bind and genes become inactive.

In mice, the mice coat colour is regulated by the *agouti* gene which, with mutated, results in mice with a yellow coat. The *agouti* gene product can also control the *melancholic 4 receptor (MC4R)* gene which is known to induce obesity when mutated. Researchers at the department of radiation oncology at the University of Duke fed mice with a folate diet which is known to regulate DNA methylation. They found that the diet conferred a protective effect preventing the mutant *MC4R* from inducing obesity highlighting the importance of DNA methylation in regulating obesity.

The researchers highlight that the methylation modification induced by the folate diet transcriptionally silences the *agouti* gene preventing the production of functional *agouti* protein. As a result, the mutant *MC4R* gene was not transcribed and thus became inactivated resulting in mice that were of normal weight. Dolinoy states that the this "epigenetic regulation serves as a link between nature and nurture" where environmental exposures can interact with the epigenome to influence phenotype.

In humans, many association studies have been conducted and DNA methylation has been shown to misregulat-

ed at genes encoding leptin, adiponectin, and insulin receptor substrate-1 which are known to regulate adipose-tissue differentiation and fatty acid oxidation. However, questions remain regarding the origin of the marks. Current research is focused on assessing whether DNA methylation misregulation is the cause or consequence of obesity. Furthermore, question remain regarding the translatability of the murine model finding to humans. For example, Cone (2000) highlight that the *agouti-MC4R* mechanism is quite well conserved between mice and human. However, further studies must be conducted to assess whether other epigenetic, genetic, and environmental interaction are also conserved.

Histone Modification

Histone protein compact the genetic material as their positive charge attracts the negatively charged DNA. In addition, histone have terminal tails that can be modified through the addition of compounds such as methyl, acetyl, and phosphate groups. Similar to DNA methylation, the quantity, location, and identity of the compound attached can alter the interaction between DNA and histones influence the degree of compactness. For example, the addition of an acetyl group can neutralize the positive charge of the histone tail minimizing its interaction with the DNA allowing the transcription machinery efficient access and ultimately activating gene expression.

Histone modification has been shown to be altered by high-fat diets and consequently shown to be involved in the regulation of adipogenesis and obesity development. Researchers at the Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology in Poland studied the changes to chromatin in a murine model and discovered that upon feeding a high-fat diet, multiple histone marks were misregulated at the genes responsible for adipocyte differentiation and proliferation. In particular, they found the accumulation of permissive histone markers such acetylation. Although the researcher highlights that an association between acetylation and obesity is postulated, it remains to be determined whether the histone modification is responsible for obesity or vice versa.

ncRNA

In addition to DNA methylation and histone modification, a large number of noncoding RNAs (ncRNA) have also been shown to underly obesity. Traditionally considered junk sequences without function, research over the years has shown ncRNA to be involved in a wide range of biological processes and diseases. They are characterized by their lack of protein-coding capability, they have been shown to be involved in adipogenesis, adipocyte differentiation and fat metabolism.

Analyzing global ncRNA levels to investigate whether ncRNAs are involved in childhood obesity, Liu Y et al (2018) found over 1000 differentially expressed ncRNA in children with obesity. Further analysis of these ncRNA revealed them to involved in a wide range of biological processes including lipid and fatty acid metabolism and adipogenesis.
Their results also indicate the regulation of DNA methylation and histone modification factors by these ncRNA further implicating epigenetic based mechanisms in obesity. The researchers highlight that although their results are predominately based on bioinformatic analysis, further validation of these ncRNA can reveal the molecular mechanism of obesity providing important strategies for diagnostic tools and therapeutic intervention.

Integrated Approach to Obesity

Research on obesity has provided evidence suggesting that genetics changes are not the only factors that regulate obesity. Although diet is also known to regulate obesity, it has been unclear as the mechanistic connection between them. However, epigenetic studies indicate that the mechanistic connection may proceed though epigenome changes indicating towards an integrated model underlying obesity. For example, environment changes, such as the diet consumed, may induce changes to the epigenome.

As a consequence, epigenome might then misregulated genes to induce obesity. However, question remain regarding the direction of interactions. Is it the genes that influence the epigenome, or the epigenome that influences the genes? Or rather, a model in which the genome, epigenome and epigenome interact in a These epigenetics changes might fill the gap of unexplained heritability in obesity.

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