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Nutritional and environmental epigenetics effects on human health and diseases

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Abstract--Both industrialized and developing nations see an alarming rise in adult-onset illnesses such as T2D and CVD. According to human and animal research, prenatal and early postnatal circumstances may alter a person's vulnerability to chronic diseases later in life. Epigenetic modulation of gene expression has been proposed as one of the processes through which early life

environment impacts future illness risk. It is possible that our understanding of the underlying mechanisms may lead us to design new intervention strategies that can lessen the burden of sickness in later life.

Keywords--DNA methylation, epigenetics, histone modifications, gene expression, human health, diseases.

Introduction

One in three fatalities worldwide is caused by NCDs, including diabetes, CVD, and metabolic syndrome. With the significant rise in prevalence of NCDs reported in nations with improving socioeconomic conditions, NCDs are becoming more relevant in low and middle-income countries. Fixed genomic variants can explain only a tiny portion of a population's variance in NCD risk. According to increasing data, prenatal and early postnatal circumstances have a crucial role in determining the risk of acquiring a broad spectrum of NCDs in later life. According to a Norwegian study, undernutrition and poverty in early life have been linked to an increased risk of cardiovascular disease (CVD) later in life. This study was the first to show a connection between poor early life nutrition and an increased risk of CVD in adults. Barker and colleagues and Hales et al. went on to link the health of British adults in their mid-thirties to their reported birth measurements (Agarwal et al., 2018; Alam, Abdolmaleky, & Zhou, 2017). The risk of cardiovascular disease, hyperlipidaemia, T2D and hypertension was significantly higher among children born at lower birth weight. Many epidemiological studies have confirmed these results, but they also showed that children with the heaviest birth weights are more likely to develop diabetes or obesity. A correlation between foetal weight gain and the risk of developing chronic diseases was first discovered in epidemiological studies (Mathur & Vyas, 2013; Muchakayala et al., 2022). Still, the 1944 Dutch Hunger Winter famine and its effects on children's health have since shown that maternal nutrition has a lasting impact on children's health throughout their lives. That timing of environmental constraints is crucial. Obesity and cardiovascular disease are more common among women subjected to famine during the Dutch Hunger Winter throughout their pregnancies (Aleksandrova, Romero-Mosquera, & Hernandez, 2017; Andersen & Millar, 2021; Andreescu, Puiu, & Niculescu, 2018).

In contrast, those exposed in the latter stages of their pregnancies were more likely to develop hypertension. In animal models, it has been reported that pregnant rats or mice are fed low-protein, high-fat or even junk food diets when pregnant or breastfeeding. For some unknown reason, the progeny of these animals show characteristics of human cardiometabolic illness, including insulin resistance, dyslipidaemia, obesity, and hypertension as they age. By altering early life nutrition, Gluckman and Hanson believe that an organism's development may be reprogrammed in response to environmental signals to improve its survival or fitness in the future (Bellanti & Settignano, 2019; Berdasco & Esteller, 2019). An organism is in danger of metabolic sickness as soon as it adapts to a new environment because of a "mismatch." NCDs have been related to increased rates

of socioeconomic transition in countries with mismatches between prenatal and postnatal environments.

Control of gene expression via epigenetics

Recent research has implicated epigenetic control of genes in the effect of early life environment on future illness risk. It may be possible to generate and sustain these developmental alterations throughout one's life using epigenetic processes while still providing the necessary variety and speed of adaption. An epigenetic alteration, which is handed down during cell division without affecting the DNA sequence, may significantly impact gene expression (Subramanian et al., 2022; Valluri et al., 2021). Examples of epigenetic processes include the alteration of histones and the production of non-coding RNAs. Each cell's function in the body is defined by its ability to access the DNA sequence, controlled by these factors together (Cai & Levine, 2019; Cavalli & Heard, 2019; Chang, Wu, & Lu, 2020) (Figure 1).

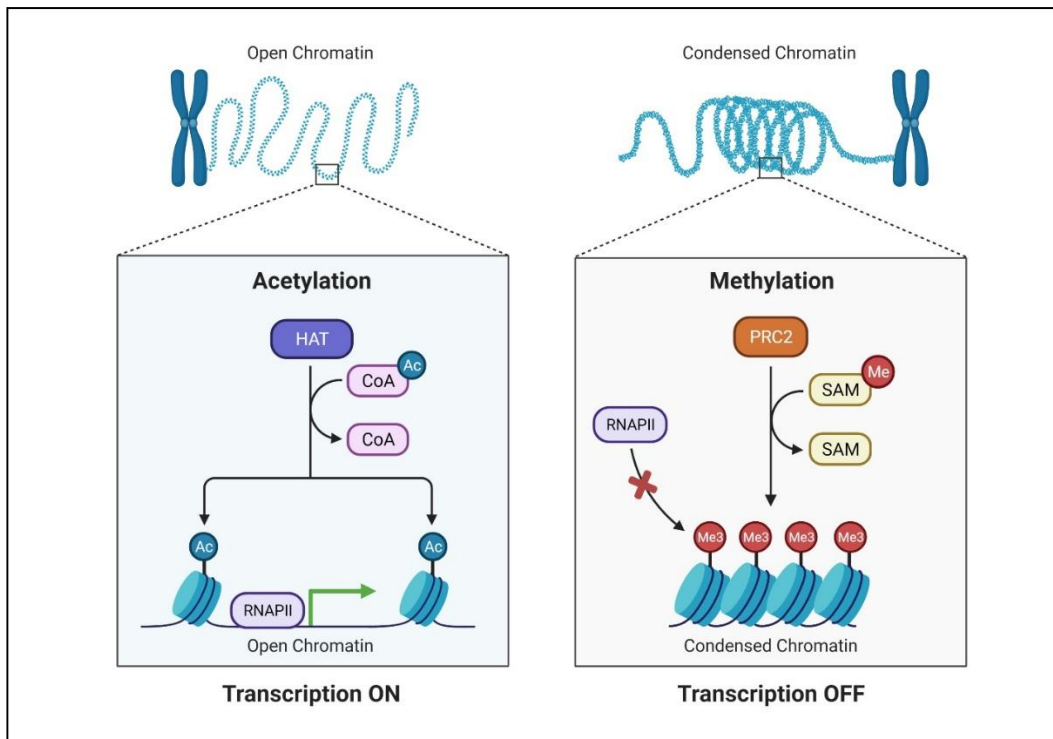


Figure 1. Epigenetic regulation on gene expression

DNA methylation

Adding a methyl group to the 5-carbon position of cytosine results in creating 5-methylcytosine, or 5-methylcytosine. Within the CpG dinucleotide sequence, cytosine methylation occurs mainly when a 5'-methylated cytosine is directly after an unmethylated cytosine. Hypomethylation is linked to gene activation, whereas hypermethylation is linked to gene silencing. DNA methylation may obstruct

transcription factor (TF) binding directly, but numerous other repressive factors that govern local chromatin alterations are thought to be recruited as a primary mechanism of action. The methylation of DNA. DNA methylation seems to be directly opposed to certain histone modifications that promote a more open and accessible form of chromatin, which has been shown to influence nucleosome occupancy and inhibit the binding of TF and Pol II (Charras & Hedrich, 2019; Choi, Han, Kwak, & Kim, 2021). It's thought that the blastocyst implantation causes a lot of DNA methylation *de novo* in the inner cell mass, leading to lineage-specific methylation patterns that persist in differentiated tissues long after the increase in sperm and egg DNA methylations during fertilisation has subsided (Vyas, Mathur, Patel, & Patel, 2017). However, global DNA methylation levels fall rapidly during the first few development days (Chellappan et al., 2018; Coppedè, 2020; Cruz-Rodriguez, Combata, & Zabaleta, 2018; Gautam, Sharma, Sharma, & Gupta, 2018) (Figure 2).

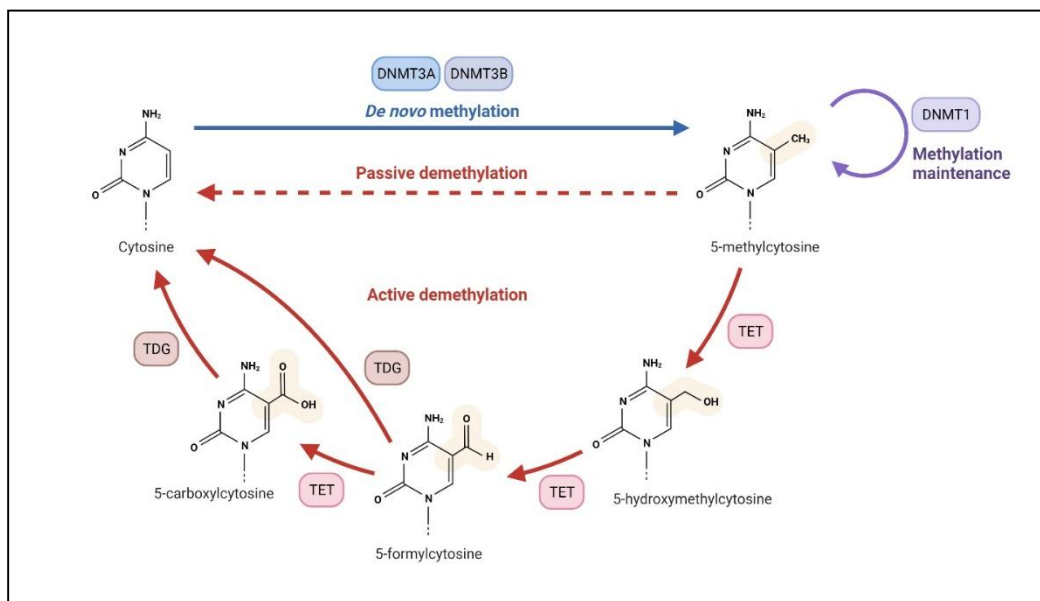


Figure 2. DNA Methylation

Histone modifications

It is the nucleosome; a structure made up of two copies of each of the four different histone proteins (H2A, H2B, H3, and H4), that serves as the foundation for all other chromatin structures. Proteins that regulate gene expression may bind to the unstructured tail of histone proteins, enabling enzymes to access specific histone modifications to be added to particular residues. Chromosome structure and biological function are controlled by histone and DNA methylation changes working cooperatively (D'Agnelli et al., 2019; Daskalakis, Rijal, King, Huckins, & Ressler, 2018).

Non-Coding RNA

A cell's transcribed RNA serves as a template for creating proteins in less than half of the cases. For both translational and transcriptional control, non-coding RNAs (ncRNAs) are vital components of the transcriptional regulatory mechanism. Translational repression and pre-mRNA degradation are possible effects of binding to the promoter region by small ncRNAs. This may lead to lower transcriptional activity or even complete transcriptional silencing. Therefore, processes like X-inactivation and imprinting must use long non-coding RNAs (ncRNAs), which coat whole chromosomes and create repressive domains that may span several kilobases (Dolcino, Friso, Selmi, & Lunardi, 2020; Donahue, 2018).

Environmental factors that affect gene expression

According to an increasing body of research, early childhood experiences have been linked to changes in the epigenome. According to this study, mother nutrition affects DNA methylation levels in the offspring of the A^{vy} mouse, which is regulated by methylation of the agouti gene's 5' ends. When dietary methyl donors and cofactors were added to the mother's diet, the methylation of the agouti gene became more pronounced. According to studies in several animal models, maternal ingestion of macro- and micronutrients may affect the methylation of essential metabolic genes in children during pregnancy. For example, pregnant women eating a protein-restricted diet had their GR and PPAR α genes hypomethylated (Ermolaeva, Neri, Ori, & Rudolph, 2018; Feinberg, 2018; Sachchidanand Pathak, 2021). There was also an increase in gene expression of nuclear receptors GR and PPAR α and metabolic activities that they control. Hypomethylation of the angiotensin receptor promoter (AGTR1B) was connected to a three-fold increase in gene expression when maternal protein restriction was implemented. ALDOSTERONE, the primary cause of hypertension, is directly influenced by AGTR1B. In light of concerns about increased energy-rich food consumption in Western and modernising societies, several studies have examined how maternal high-fat feeding impacts DNA methylation in the child. According to Hoile and colleagues, a high-fat diet during pregnancy lowered FADS2 expression and altered the methylation of crucial CpG nucleotides in the promoter of the gene's child. Adults who ate a high-fat diet for nine weeks saw a transient increase in FADS2 expression and methylation. Even if the underlying cause is abolished, early-life alterations persist, but adult systems are significantly more challenging to influence outside the developmental window (Feng & Lou, 2019; Fu et al., 2019; Wadhwa et al., 2020). " Studies have indicated that epigenetic plasticity extends beyond the early intrauterine period into postnatal life. One of the genes involved in appetite regulation, the POMC promoter, has been hypermethylated in neonates who had been overfed. Hypermethylation of the POMC promoter inhibited increased POMC expression despite high levels of leptin and insulin in the blood. When folic acid is taken in the juvenile-pubertal period, it has been demonstrated to increase promoter methylation in rats given protein-sufficient or limited diets throughout pregnancy, which resulted in lower PPAR α expression and uterine oxidation. Taking folic acid before puberty has been linked to an increased risk of breast cancer in pre-

pubescent females (Fyfe, 2018; Garcia-Martinez, Zhang, Nakata, Chan, & Morey, 2021).

The influence of early childhood experiences on the epigenome

A slight reduction in CpG methylation in the IGF2 imprint regulatory region has been found in investigations of the Dutch Hunger Winter cohort in humans. Still, no changes in CpG methylation have been seen in late-gestational exposure to hunger. Many additional genes showed the same trend, with exposure during the periconceptional period linked to minor DNA methylation changes in various loci (including MEG3, leptin, ABCA3 and IL-10) but not exposure later in pregnancy not showing similar changes (Gomez, 2019; Gupta et al., 2018; Hanahan, 2022; Jha et al., 2022).

There may be an epigenetic component to long-term gene expression and metabolism changes in the kid due to early life experiences. CpG sites may be difficult to edit in live creatures, increasing the difficulty of determining the causality of a single CpG change. There is some evidence from research on Dutch Hunger Winter inhabitants that methylation levels in peripheral blood may be used as a surrogate for disease risk in other important cell types (Harsanyi, Zamborsky, Krajciová, Kokavec, & Danisovic, 2020; Harvey, Chen, & Jarosz, 2018). CpG location in the promoter of the RXR was shown to be linked to childhood obesity, accounting for nearly a fifth of the variation in childhood fat mass. These results suggest that it may be able to identify those who are more likely to develop chronic illness before symptoms appear, which might lead to better treatment options (Devi et al., 2018; Gupta et al., 2021; Hübel, Marzi, Breen, & Bulik, 2019; Hwang, Aromolaran, & Zukin, 2017).

Conclusions

The mother's diet has been linked to changes in gene expression patterns in metabolically essential parts of the foetus. Diabetes, high cholesterol, hypertension, and cardiovascular disease are related to these disorders' effects on growth and metabolism (CVD). The discovery of disease-risk-associated epigenetic markers opens the door to new avenues of prevention and treatment. The number of people diagnosed with non-communicable diseases (NCDs) is on the rise, yet therapy is expensive and can only control the sickness. Individuals' well-being and financial burden might be reduced by employing epigenetic biomarkers to predict their disease risk and developing a more effective preventative treatment plan.

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Conflict of interest

There is no conflict of interest, the authors declare.

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