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Epigenetic Effect Of The Prenatal Environment On Fetal Development And Transgenerational Epigenetics.

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Abstract: Epigenetics refers to the changing in gene expression without changing the underlying nucleotide sequence. This includes the addition of compounds to DNA (DNA Methylation), addition of compounds to other proteins (Histone modifications), and Non-Coding RNA. The debate between nature and nurture is probably as old as time itself. How much of our identity is shaped due to the environment, and how much of it is shaped due to our genes? The bridge linking these vastly different factors is environmental epigenetics. This paper aims to outline some examples of the effects the prenatal environment can have on a fetus even years after its birth and factors controlled by transgenerational epigenetics, as well as review research done in the field.

Keywords: Transgenerational epigenetics, Environmental epigenetics, Fetal development.

I. INTRODUCTION

In 1809, French geneticist, Jean-Baptiste Lamarck proposed a theory which one might consider to be the oldest reference to environmental epigenetics. This was called the “theory of inheritance of acquired characteristics”- or simply- Lamarckism. In his theory, Lamarck stated that physical traits acquired through the environment can be passed from parent to offspring. This idea- although it quickly dismissed back then- is the basis of modern day transgenerational environmental epigenetics.

Environmental epigenetics studies how environmental factors such as diet, stress, exposure to toxins, et cetera, control gene expression. Many studies have shown that the prenatal environment has both short-term and long-term effect on physiological health.

II. IMPORTANT HYPOTHESES AND THEORIES.

There are three major hypotheses that are central to the idea of prenatal environmental epigenetics. One is the fetal programming theory, proposed by Barker in 1995. The fetal programming theory suggests that exposure to specific stimuli in sensitive time frames in the developmental period of a fetus will show its physical effects in the extrauterine environment. The Developmental Origins of Health and Disease (DOHaD) theory (Silveira, 2007) is along similar lines, as it talks about how in utero conditions play a major role in dictating the health of the fetus.

Barker also coined the term for the Thrifty Phenotype hypothesis, which draws a connection between susceptibility to type 2 diabetes and heart disease and low neonatal weight. However, Barker noted that the hypothesis was not specific to epigenetics and took into consideration other factors such as genetic predisposition. In 2001, Baker and Hales updated this theory, stating that it can be considered an evolutionary adaptation. The malnutritional in utero environment allows the fetus to preserve crucial organs to prepare for a much more malnutritional post-natal environment. This is an example of a predictive adaptive response (PAR).

III. STUDIES ON PRENATAL ENVIRONMENT EPIGENETICS.

In 1977, Ravelli et al. studied 300,000 Dutch men who were born during WW2. Their mothers were exposed to malnutrition (due to the Dutch winter famine) at different times of their pregnancy. A perplexing finding was that the offspring of women who were exposed to these factors in the first 6 months of their pregnancy had higher incidence to obesity, cardiovascular disease and hyperlipidemia as compared to those exposed to these factors in the last 3 months of their pregnancy. This study is a common example used to model a PAR. The fetus, in it malnutritional environment, would obviously predict that the postnatal environment would be the same. Therefore, the body would not have prepared to be exposed to nutrition, and would withhold more nutrients, which, in turn, would lead to obesity.

Autism Spectrum Disorder (ASD) is a type of developmental disorder that arises in the first 3 years after childbirth. Soon Choi et al. exposed pregnant mice to Valproic Acid (VPA). The outcome was mice born with Neural Tube Defect (NTD), which resulted in a crooked tail phenotype, exhibiting ASD-like behavior. This can be explained by the fact that VPA is a known inducer of NTD. By investigating how reversible these conditions are, Turpin found that feeding polyunsaturated fatty acids to mice prenatally exposed to VPA can act to reverse the autism-like effects of VPA on the cerebellum regions of the brain, which lead to ASD and ASD-like disorders to begin with.

One of the most popular examples used to understand exemplify the system of transgenerational epigenetic variations due to the in utero conditions is that of glucocorticoids (GCs) which are a group of steroids that are a major component of the stress response. A study was conducted on Rwandan women who were pregnant during the Tutsi genocide and experienced trauma as a result of it. The factors measured were cortisol (a type of GC) levels in blood plasma, and methylation of *NR3C1* and *NR3C2* promoter regions (both of which are GC receptor genes) in 25 Rwandan women and their children who were exposed to the Tutsi genocide, and 25 Rwandan women and their kids, who were not exposed to the genocide. On comparison, they found that the cortisol levels were higher in the mothers and their offspring who were exposed to the genocide, and that NR3C1 and NR3C2 were more methylated in them as well. We can hence deduce that PTSD and stress were passed down from mothers to offspring when they are exposed to traumatic events during their pregnancy.

IV. STUDIES ON TRANSGENERATIONAL EPIGENETICS

Transgenerational epigenetics refers to the study of inherited changes in gene expression without any change to the genetic sequence. This inheritance can be paternal or maternal.

When it comes to paternal epigenetics, a study by Brian Dias et al. gave intriguing results. Dias exposed a group of male mice to acetophenone, a chemical with a pleasant, almond-like scent. This would be repeated for five times each day. After 3 days of receiving this treatment, the mice would get scared just by smelling the acetophenone. After mating with female mice, the offspring of the mice also showed similar responses to the scent of acetophenone. This continued for a third generation of mice as well. Additionally, all these mice had enlarged M-17 glomeruli, which is the connection point between the olfactory bulb and the acetophenone

sensitive neurones. It was found that the sex of the mice had no correlation to their gene expression, therefore it is not considered sex specific.

The Avon Longitudinal Study of Parents and Children (ALSPAC) conducted by Pembrey et al. shows a great example of sex-specific correlation in transgenerational epigenetics. Pembrey found that the sons of 166 men who began smoking in the prepubescent ages (before the age of 11) have a higher than Body Mass Index (BMI), but not their daughters. Furthermore, it was also noted that the offspring of men who began smoking between ages 11-13 did not show high BMIs. The researchers theorize that this may be a genetic pleiotropy, where the gene that makes the sons over eat also made the fathers predisposed to an early onset of smoking.

V. CONCLUSION

The field of environmental epigenetics offers great insights into the connections between our genes and the environment. By exploring how prenatal factors influence gene expression, researchers can better understand the mechanisms that lead to various health conditions. The implications of these findings are vast, affecting fields ranging from public health to developmental psychology. Understanding the mechanisms of epigenetic inheritance can lead to improved strategies for preventing and treating diseases that have roots in early development and environmental exposure from the parents. As research progresses, it is crucial to consider both the genetic and environmental components that shape our health and behaviour, embracing a more holistic view of human biology that integrates the principles of epigenetics.

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