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CLINICAL NUTRITION RESEARCH

Nutrition, Epigenetics, and Diseases

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Increasing epidemiological evidence suggests that maternal nutrition and environmental exposure early in development play an important role in susceptibility to disease in later life. In addition, these disease outcomes seem to pass through subsequent generations. Epigenetic modifications provide a potential link between the nutrition status during critical periods in development and changes in gene expression that may lead to disease phenotypes. An increasing body of evidence from experimental animal studies supports the role of epigenetics in disease susceptibility during critical developmental periods, including periconceptional period, gestation, and early postnatal period. The rapid improvements in genetic and epigenetic technologies will allow comprehensive investigations of the relevance of these epigenetic phenomena in human diseases.

Key Words: Nutrition, Reprogramming, Development, Epigenetic, Disease

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Introduction

Many human diseases that appear in adulthood are related to growth patterns during early life. It is now recognized that early-life nutrition and other environmental factors play key roles in the pathogenesis and in the predisposition of specific human diseases. In this regard, in 1995 Dr. Barker wrote: "The fetal origins hypothesis states that fetal undernutrition in middle to late gestation, which leads to disproportionate fetal growth, programs later coronary heart disease."[1]. The word "program" illustrates the idea that the environmental stimuli received during critical periods of early fetal development can generate permanent changes in body structure and function that affect the homeostasis of specific organs in the adult life [2]. The responsiveness of a growing body to external cues is defined as developmental plasticity. Developmental plasticity derives from the ability of our genes to organize different ranges of physiological or morphological states in response to environmental conditions during fetal development. In this review we focus on particular situations in human and experimental animal models to underline the link between nutritional and environmental stimuli during critical periods of the early development and the susceptibility to disease development in the adult life.

Dutch Famine Birth Cohort

Insights in the importance of nutritional supply during a critical period on long-term disease outcome were gained from the Dutch Famine cohort. The Dutch Famine cohort is one of the most well-known cohorts that have been used to investigate the effects of prenatal undernutrition in humans. During the Nazi occupation from November 1944 to May 1945, food supply was extremely limited in some parts of the Netherlands. Daily rations during this famine period started at less than 1,000 kcal in November 1944, and decreased to about 500 kcal by April 1945. This six month food shortage had a major impact on particular situations, such as ongoing pregnancies. From 1998, the Dutch Famine Birth Cohort Study began reporting the outcome of pregnancies that occurred during this famine period and the consequences of massive maternal undernutrition on the offspring on a long-term scale [3-5]. Results showed an increased risk of cardiovascular diseases 40-50 years later in those children born to mothers who experienced extremely severe undernutrition during the first trimester of pregnancy [6]. The incidence of cardiovascular diseases was 2 times higher in this group compared to the control cohort [6]. Also, the serious nutritional deprivation increased the risk of metabolic disorders and breast cancer decades later in this cohort [7-9]. Notably, depending on the period of starvation (early versus late pregnancy, and preconceptional versus postnatal undernutrition) marked differences in disease outcomes were observed, indicating that the first trimester of pregnancy is particularly vulnerable to disease outcome in adulthood.

Why Your DNA Isn't Your Destiny

Another interesting epidemiological study pointed out the importance of nutritional status during puberty and its impact on the offspring's health, by investigating if the availability of food to one generation affected longevity and health of the descendants. This study conducted by Dr. Bygren, investigated the long-term effects of feast and famine on children growing up in the isolated Swedish county of Norrbotten, with the goal to unravel whether "Parents' experiences early in their lives change the traits they passed to their offspring" [10]. In the 19th century, Norrbotten was so isolated that if the harvest failed, people starved. Harvest failures occurred erratically, causing famines in 1800, 1812, 1821, 1836 and 1856. Bygren and colleagues found that if an individual went through a famine as a teenager, his or her grandchildren would have shown higher mortality risk ratio, but only if the grandchildren were the same sex as the grandparent who starved [10,11]. Starvation of a male only changed his grandson's mortality risk and starvation of a female only changed her granddaughter's mortality risk [10,11].

Early nutrition and onset of metabolic phenotype in adult

The three main insights of a number of studies from the Dutch and Norrbotten's cohorts are: 1) there may be critical developmental time windows where overnutrition or undernutrition may promote or impede disease development; 2) epigenetic factors can be modified by hunger exposure during these critical time windows; and 3) acquired epigenetic alterations are passed on to offspring. To better address these points, various animal models have been developed to explore whether nutritional or environmental modifications over critical developmental windows affect lifelong disease risk. It has been shown, for example, that overfeeding dams during gestation and lactation with high-caloric diet or reducing the number of pups in a litter could indirectly overnourish pups. Table 1 and Table 2 summarize some of the results observed in the offspring's phenotype induced by specific maternal dietary effects in different developmental time windows and in different experimental models. From these animal studies we can conclude that maternal overnutrition or undernutrition may act as an early mechanism of programming of the developing embryo/fetus, and may instruct a status of 'metabolic stress', restricting early embryonic cell proliferation and the generation of appropriately sized stem-cell pools. These observed phenotypic changes are dictated by the epigenetic-based molecular mechanisms that govern stability, transfer and expression of the eukaryotic genome.

Epigenetics

Since the Human Genome Project completed sequencing the 3 billion chemical base pairs that make up human DNA in April 2003, it became clear not only that we are able to read nature's complete genetic blueprint, but also that the information stored in the sequence of the DNA is not enough *per se* to completely explain human development, physiology and disease. The field dedicated to decipher the heritable features that complements the genetic information stored in the DNA sequence is termed "epigenetics". The prefix epi- is derived from the Greek preposition ἐπί, meaning above, on or over. Formally, epigenetics refers to the study of heritable changes in gene ex-

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Table 1. Experimental animal models with maternal dietary modifications during development or early life, and their impact on phenotype of offspring

Species	Dietary modification	Time window of dietary modification	Observations in offspring	Reference
Mouse	Maternal low protein diet (9% vs 19% control)	One ovulatory cycle (3.5 days) prior to mating	Abnormal anxiety-related behavior in offspring; elevated systolic blood pressure	[50]
Rat	Maternal low protein diet (9% vs 19% control)	Preimplantation period (0-4.25 day postcoitum)	Low birth weight; altered postnatal growth; hypertension	[51]
Mouse	Maternal obesogenic diet (OD, 10% simple sugars, 20% animal lard, 28% polysaccharide, 23% protein, 4.5 kcal/g) vs standard chow diet (SD, 7% simple sugars, 3% fat, 50% polysaccharide, 15% protein, 3.5 kcal/g)(52) Maternal hypercaloric diet (OD, 16% fat, 33% sugar) vs standard chow (SD, 3% fat, 7% sugar)(53)	6 weeks prior to mating – gestation - lactation 1. OD-OD-OD 2. SD-SD-SD 3. OD-OD-SD 4. SD-SD-OD	Dysmetabolic and non-alcoholic fatty liver disease (NAFLD) phenotype in offspring of postnatal OD	[52] [53]
Rat	Maternal high fat diet (HF diet: 60% kcal from fat vs CHOW diet: 17% kcal from fat)	Gestation and lactation 1.CHOW-CHOW 2.HF-HF	Increase in susceptibility to diet-induced obesity	[54]
Rat	Maternal high-fat diet (HF diet: 60% kcal from fat vs CHOW diet: 13.5%)	Gestation and lactation 1.CHOW-CHOW 2.CHOW-HF 3.HF-CHOW 4.HF-HF	Increase in adiposity, leptin and impaired glucose intolerance in postnatal HF offspring	[55]

OD: obesogenic diet, SD: standard chow diet, NAFLD: non-alcoholic fatty liver disease, HF: high fat diet, CHOW: chow diet.

Table 2. Rodent small litter models of postnatal overnutrition, and their impact on metabolic phenotype

Species	Litter size	Observations in pups from small litter	Reference
Mouse	3:9 (small:control)	Increase in body weight; impairment in glucose tolerance; decrease in insulin sensitivity in the heart	[56]
Mouse	4:9 (small:control)	increase in body weight and fat mass; decrease in physical activity and energy expenditure in females only	[43]
Mouse	4:9:20 (small:control:large)	Increase in body weight, adiposity (number and size) and blood insulin level; impaired glucose tolerance	[57]
Rat	4:10:16 (small:control:large)	Increase in body weight and body fat weight	[58]
Rat	3:10 (small:control)	Increase in body weight and body fat at postnatal day 21 and 180; central leptin resistance in adult life (postnatal day 180)	[59]
Rat	3:10:19 (small:control:large)	Early postnatal hyperinsulinemia; decreased glucose tolerance; increased susceptibility to streptozotocin-induced diabetes in adulthood	[60]
Rat	4:12:18 (small:control:large)	Increase in body weight; reduction in pancreatic glucose responsiveness; differential expression of pancreatic islets genes (13 genes) at postnatal day 26, 10 of them were maintained by postnatal day 110	[61]

pression that are not caused by changes in the DNA sequence [12]. In a more practical sense, epigenetics includes the study of DNA modifications, the post-translational changes of the protein constituents of the chromatin, namely the histones, the chromatin modifications that appear to define biologic states in local regions of chromosomes, and the interaction of microR-

NAs with the genome [13]. Recent epigenetic studies have, for example, highlighted the mechanistic nature of the interactions between DNA and the enzymes that perform DNA replication, transcription, recombination, and repair [14].

DNA methylation

DNA methylation is a common modification in mammalian genomes and is considered a stable epigenetic mark transmitted through DNA replication and cell division [15]. Methylation is a covalent binding of a chemical methyl group to the cytosine (C) base in DNA sequence, specifically at CpG (cytosine-phosphate-guanine) dinucleotides. Methylation of C is typically associated with the 5' end of gene sequences, where CpG dinucleotides islands are particularly dense. Hypermethylation of the CpG islands is associated with transcriptional repression, while their hypomethylation is associated with the transcriptional activation of surrounding genes [16]. DNA methylation established during development and early postnatal life plays critical roles to regulate cell- and tissue-specific gene expression and genomic imprinting. Genomic imprinting is an epigenetic phenomenon in which the expression of a gene copy depends on its parent of origin [15,17], the significance of DNA methylation in genomic imprinting was highlighted in CpG islands of imprinted genes such as IGF2 and H19 [18]. In normal cells, the paternal IGF2 and maternal H19 gene are expressed while maternal IGF2 and paternal H19 are silenced by DNA methylation [19]. *De novo* DNA methylation is catalyzed by the DNA methyltransferases (DNMT) 3A and 3B, whereas DNA methylation is maintained after the replication of the DNA by DNMT1, which methylates hemi-methylated DNA [17]. Once established, DNA methylation is essentially maintained throughout life; however, a gradual hypomethylation occurs during aging, and it has been linked with some types of cancer [20].

Histone modification

The DNA in the cells is packaged as chromatin. The basic unit of chromatin is a nucleosome, which comprises 147 bp of DNA wrapped around a core of 8 histone proteins (two copies of histone H2A, H2B, H3 and H4) [21]. The N-terminal tails of the histones are subject to post-translational modifications including acetylation, methylation, ubiquitination, sumoylation, and phosphorylation [22]. Histone modifications lead to structural changes of the chromatin, and to the recruitment of effector proteins, for example transcription factors, which in turn bring about specific cellular processes by modulating target gene expression. Histone acetylation is exclusively associated with active and open chromatin states, while the methylation of lysine residues in the N-terminal of histones can either be an active or repressive mark depending on the specific lysine involved [23]. Many families of histone-modifying enzymes have been identified, including histone acetyl transferases, deacetylases, methyltransferases, and demethylases [24].

Non-coding RNAs

Non-coding RNAs (ncRNAs) have been implicated in the epigenetic regulation of gene expression by gene silencing or target mRNA degradation. Recent studies have shown that human miRNAs can induce chromatin remodeling [25,26], suggesting that DNA methylation, histone modification and miRNAs may work in concert to regulate gene expression.

Developmental plasticity

During the development of multicellular organisms, different cells and tissues acquire different programs of gene expression. It is well recognized that a series of precisely timed and regulated epigenetic changes are required to ensure the proper development of complex organisms like humans [15,27]. At the morula stage, an early step of embryonic development, DNA demethylation occurs to erase all of the parent-of-origin methylation marks, except those of the imprinted genes. This allows for the inheritance of parental-specific monoallelic expression in somatic tissues throughout adulthood. This demethylation phase is followed by the *de novo* DNA methylation of the genome to establish the proper methylation patterns of the growing organism [28]. In such a way, as the embryo grows the offspring acquires their appropriate epigenetic features. In parallel to these changes occurring in somatic cells, another set of genomic reprogramming takes place in the cells of the germ line during gametogenesis [29]. In fact, during gonadal sex determination, primordial germ cells undergo genome-wide demethylation, which erases previous parental-specific methylation marks. Afterward, for example in the male germ line, paternal methylation marks occur in specific genes in the gonocytes that subsequently will develop into spermatogonia. Conversely, the female germ line establishes maternal methylation marks of imprinted genes at a later stage. In addition to DNA methylation, histone modifications are thought to play a role in the establishment of both sex-specific and non sex-specific marks because an extensive loss of histone methylation and acetylation occurs along with the loss of DNA methylation at the morula stage [30]. Epigenetic marks assure the proper expression of the imprinted

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genes throughout the embryonic development. For example, genomic imprinting results in the monoallelic, parent-of-origin dependent expression of genes specifically required for key developmental steps. It is predictable from this scenario that the aberrant methylation of imprinted genes, mostly loss of imprinting (LOI) in the early stages of development, can alter the expression of critical genes, and then may bring out birth defects and adulthood diseases such as cancer [31]. In this regard, given the nature of the monoallelic expression, imprinted genes are particularly susceptible to the effect of epigenetic aberrations. In addition, for the strict dependence of these early steps of development to nutritional support, inherited and acquired epigenetic marks are particularly vulnerable to the interference coming from environmental stimuli [32].

Early life nutrition and altered epigenetic regulation

Due to the dynamic changes of the epigenetic regulation in development, particularly during gametogenesis and early embryogenesis, the epigenome displays labile nature, which allows it to respond and adapt to environmental stressors, including nutritional modification. For instance, periconceptional supplementation or restriction of the maternal diet with betaine, choline, folic acid, methionine, or vitamin B-12 in experimental models have been shown to affect the establishment of DNA methylation patterns, altering the gene expression and phenotype of the offspring [33]. Three main experimental approaches are in use to better understand the underlying mechanism by which nutritional modifications affect the epigenetic profile during critical developmental windows: 1) the study of epigenetically labile genes, such as the insulin-like growth factor 2 (IGF2) gene; 2) the use of specific, natural animal models, such as the *agouti* mice; and 3) the targeting of a specific organ that is central for energy metabolism using dietary modification.

Insulin-like growth factor II (IGF2)

IGF2 is a key protein in human growth and development [34]. The IGF2 gene is maternally imprinted and is one of the best-characterized epigenetically regulated loci [32]. The imprinting of this locus is maintained through the methylation of a DNA sequence named the differentially methylated region (DMR), the hypomethylation of which leads to bi-allelic expression of the IGF2 gene. As illustrated by retrospective studies from the Dutch famine cohort [35] as well as in experimental animal studies [36-38], the IGF2 gene has been shown to be characterized by a labile methylation pattern depending on the nutritional or environmental stimuli received by the growing organism during the early life. Table 3 summarizes some data that support the observed developmental plasticity of the IGF2 locus. Notably, post-weaning mice fed a methyl-deficient diet exhibit permanent LOI and dysregulated expression of the IGF2 gene [37], suggesting that both childhood and maternal diet contribute to the LOI in the IGF2 locus in humans.

Agouti model

The *agouti* mouse has been extensively used to investigate the phenotypic impact of the nutritional modification during critical developmental periods, and the environmental influence on the fetal epigenome [39]. The *agouti viable yellow* (A^{vy}) locus regulates mouse coat color; more importantly, the

Table 3. Effect of maternal dietary modifications on imprinted gene, IGF2

Species	Modification during development	Time winnow for the modification	Observations in offspring	Reference
Human	Famine (Dutch Famine cohort)	Periconceptional period	Decrease in methylation of CpG dinucleotides in the IGF2 nearly 60 years after	[35]
Human	Supplementary folic acid use	Periconceptional period	Higher methylation of the IGF2 differentially methylated region (DMR)	[62]
Rat	Maternal low protein diet (8% vs 20 %) and high fat diet (45% vs 10%) after weaning	2 weeks prior to mating – gestation - lactation	Increase in adipose tissue Igf2 mRNAs by the low protein prenatal diet	[38]
Rat	Maternal low protein diet (9% vs 19% control)	Preimplantation period	Decrease in H19 imprinted gene expression in male blastocysts; reduction in H19 and Igf2 expression in male fetal liver at day 20 of gestation	[36]
Mouse	Methyl deficiency (methionine, choline, folic acid and vitamin B12)	60-day post-weaning	Loss of imprinting of Igf2	[37]

Table 4. Effects of maternal diet or environmental factors on yellow agouti offspring

Dietary or environmental modification	Observations	Reference
a/a females mated with the same strain of mottled yellow or pseudoagouti A^{vy}/a males; methyl-supplemented diets (folic acid, vitamin B12, betaine, and choline) to pregnant dams	Increase in *agouti*/black mottling in the direction of the pseudo-agouti phenotype	[40]
A^{vy}/a females mated with *a/a* males; methyl-supplemented diets (2 different diets) to pregnant dams	Increase in DNA methylation in the *agouti* LTR (long terminal repeat); change the phenotype of offspring in the healthy, longer-lived direction	[63]
F0 A^{vy}/a dams mated with *a/a* males; F1 A^{vy}/a female mated to a/a brother; F2 A^{vy}/a female mated to a/a brother; methyl-supplemented diets (folic acid, vitamin B12, betaine, and choline) to pregnant dams	Average A^{vy}/a coat color was darker in the methyl-supplemented diet group; epigenetic phenotypes are maternally heritable, but no cumulative effect of supplementation across successive generations on coat color; prevention of transgenerational amplification of obesity by methyl-supplementation	[64,65]
a/a females mated with A^{vy}/a males; 250 mg/kg diet of genistein for 2 weeks prior to mating, gestation and lactation	Coat color of A^{vy}/a offspring shifted toward pseudo-agouti phenotype	[66]
a/a females mated with A^{vy}/a males; 50 mg/kg diet of bisphenol A (BPA) for 2 weeks prior to mating, gestation and lactation	Coat color of A^{vy}/a offspring shifted toward yellow by decreasing CpG methylation in an intracisternal A particle retrotransposon upstream of the *Agouti* gene	[67]

product of the *agouti* gene interferes with the regulation of body weight at the level of the hypothalamus. DNA hypomethylation of the *agouti* gene promoter results in the accumulation of the *agouti* protein; as consequence, the mouse develops a yellow coat color as well as obesity. Conversely, hypermethylation of the promoter reduces the level of the *agouti* protein, and this, consequently, results in mice with lean phenotype and brown coat color. Interestingly, feeding *agouti* female pregnant mice with a diet enriched with methyl donor supplementation such as folic acid, vitamin B12, choline and betaine has been shown to modify the phenotype of their heterozygote offspring [40]. This effect was confirmed to be mediated by the hypermethylation of the A^{vy} promoter in the offspring of supplemented dams [41]. Table 4 provides additional evidences that specific maternal dietary treatments or environmental factors affect the phenotype of the *agouti* offspring through epigenetic mechanism.

Hypothalamic DNA methylation

The central brain region integrates various peripheral signals to regulate energy balance [42]. The hypothalamus plays a key role in the regulation of food intake and energy expenditure. For these reasons, the hypothalamus is an excellent organ candidate to study the epigenetic changes that mediate the developmental reprogramming of energy metabolism. Not surprisingly, maternal overnutrition [43-46] and undernutrition [47,48] have been shown to alter hypothalamic DNA methylation. These changes in DNA methylation have been reported to persist from early life to adulthood [43,46], affecting the overall metabolism in the adult.

Conclusion

Developing organisms seem to have a wide range of susceptibility to epigenetic changes [49]. Appropriate dynamics in epigenetic modifications are essential for embryogenesis, early fetal development and early postnatal growth. Consequently, the inadequate establishment of epigenetic modifications during critical developmental periods due to changes in the maternal diet or other environmental factors may induce pediatric developmental diseases and even affect health in adulthood. Since much of the reprogramming that occurs during early life may go unrecognized until adulthood, a better understanding of the interplay between genetic and epigenetic interaction in critical time windows of development would improve our ability to determine individual susceptibility to a wide range of diseases.

Conflict of interest

We declare that we have no conflict of interest.

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