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Impact of genetic and epigenetic factors from early life to later disease

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Abstract

There is ample evidence that subtle changes in the early environment, not restricted to the fetal period but expanded to the plastic phase of early development, influence adulthood disease appearance. There is also evidence that genetic background resulting from our evolution is an important contributor to susceptibility to perinatal imprinting. However, rapid adjustment and optimization, at times necessary for survival, require a type of plasticity that the genome sequence alone cannot achieve. Without changing the genomic backbone, epigenetic modulation, in reaction to a given environment, results in functional adaptation of the genomic response. Evolutionally acquired genomic susceptibilities and environmentally induced epigenomic modulations occurring early in life impact on later development of human diseases.

1. Introduction

A landmark publication entitled "Developmental Origins of Health and Disease" [1] compiled all the evidence on how subtle changes in the early environment, not restricted to fetal period but expanded to the plastic phase of early development, influence later disease acquisition in adulthood. Studies in human subjects and animal models have shown that the early environment modulates or "programs" key hormonal systems involved in growth, metabolism, coping-with-stress mechanisms, and reproduction. Here, we review the results of early programming on late chronic disease outcomes, particularly from the viewpoint of integrating genetics and epigenetics that interact particularly strongly in the sensitive stage of early life.

2. The thrifty phenotype and early programming

Although initially prevailing opinion underlined genetics as a driver in type 2 diabetes mellitus expressed in Neel's concept (thrifty genotype, see later), the preponderance of nature vs nurture has since been challenged [2]. In 1992, Hales and Barker [3] confronted the 30-year–older "thrifty genotype" theory and proposed a new hypothesis to explain the causes of type 2 diabetes mellitus that points to nutritional conditions in early life. The thrifty phenotype hypothesis suggests that environmental factors, acting during gestation and/or early postnatal life, such as malnutrition, might promote later risk of type 2 diabetes mellitus. In the thrifty phenotype, type 2 diabetes mellitus and related symptoms arise if the metabolic program is set to "thrift" and does not match the Westernized environment encountered in later life. These authors reported a positive association between low birth weight and later cardiovascular disease (CVD) as well as type 2 diabetes mellitus, postulating that, in poor surrounding environmental conditions, a pregnant woman will modify her in utero environment so that her unborn child can better survive by adapting an appropriate growth rate through nutrient intake. However, when then exposed to an environment of plenty, these individuals are more prone to develop obesity and type 2 diabetes mellitus. Individuals with a thrifty phenotype tend to have a smaller body size, lower metabolic rate, and reduced level of behavioral activity. Once established, the acquired metabolic phenotype is maintained through the lifetime of an individual [4].

3. Fetal, infant, and childhood growth

There is ample evidence that later-life CVD development can be predicted, at least in part, by early-life events. Children of lower socioeconomic status [5], born from

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mothers who experience pregnancy-induced hypertension or who smoke throughout pregnancy, and those with a low or high birth weight [6-9], fed high-sodium diets during infancy or who are obese during childhood and adolescence are more prone to hypertension [10], type 2 diabetes mellitus, and dyslipidemia. The intrauterine environment appears to be a considerable determinant of body fat mass of an individual later in life and becomes a source of concern, particularly for societies in transition from sparse to abundant nutrition or in poorer parts of industrialized countries where malnutrition is prevalent. However, a U-shaped relationship between birth weight and several components of the metabolic syndrome was confirmed recently, even in Western, well-nourished, and full-term newborns; and it was demonstrated that postnatal weight gain was the dominant factor associated with the high risk of developing such factors as obesity, hypertension, and dyslipidemia. Furthermore, it has been observed that changes in perinatal nutrition program the development of relative fat mass and the regulation of appetite in adult life. Recently, some proposed that the thrifty phenotype is also adaptive in the longer term, by preparing the organism for its likely adult environment. However, the concept of early programming appears to be complex. Thus, the thrifty phenotype should be considered as the capacity of offspring to respond to environmental information during early ontogenetic development and is the consequence of 3 different adaptive processes: niche construction, maternal effects, and developmental plasticity [11]. Although developmental plasticity represents adaptation by the offspring, both niche construction and parental effects are sequels of parental rather than offspring fitness.

Offspring may be exposed to poor maternal metabolic control (gestational diabetes), maternally derived toxins (smoking), low maternal social status (small size), and exposure to mismatches between in utero and early life. For instance, dynamic changes in body weight early in life have to be taken into account. A series of predictive adaptive responses is thought to represent strategies for maximizing the chances of postnatal survival based on the anticipation of a particular adult environment. A mismatch between early and adult environments increases the risk of adult diseases [12]. Thus, preferential "catch-up fat" plays a role in the development of hyperinsulinemia with a disproportionally higher rate of body fat recovery than of lean tissue [13]. There is also evidence that a positive association between birth weight and later body mass index preferentially represents an association of birth weight and lean rather than adipose tissue. Thus, even if people who were small babies tend to have a lower body mass index in adult life, they also seem to have a disproportional excess of abdominal adipose tissue compared with other locations such as the extremities.

Clearly, the relationships between pre- and postnatal nutrition and their metabolic consequences are complex and extend beyond a mechanistic mismatch paradigm. We recently assessed whether exposure to a high-sucrose diet during fetal life influences the responses to high-sucrose diets in later life in a rodent genetic model of the metabolic syndrome and showed that maternal high-sucrose feeding elicited a variety of subtle effects but did not lead to predictive adaptive protection from most high-sucrose–induced metabolic derangements [12].

Early-life excess weight gain together with physical inactivity may evoke increased systolic blood pressure in adolescents, particularly among boys in industrialized countries [10]. Although the exact endocrine pathogenetic pathways are still poorly understood, key players appear to be the thermogenic effector systems in skeletal muscles mediated by substrate cycling between de novo lipogenesis and lipid oxidation under the control of insulin, leptin, adiponectin, norepinephrine, triiodothyronine, and other hormones. Studies of experimental rodent models teach us the importance of mismatched prenatal and postnatal environments provoking misprogramming of metabolic and signalling pathways [14,15].

4. The thrifty genotype

The hypothesis of the thrifty genotype was first proposed by anthropologist James V Neel [16] in 1962 to explain the high incidence of obesity and type 2 diabetes mellitus among the Pima Indians of the southwestern United States. Neel put forward the idea that many diabetics carry allelic variations in a small number of genes that would make them "exceptionally efficient in the intake and/or utilization of food." Evidence for a genetic determinant of obesity has increased over the years. Recent whole genome association studies [17,18] have identified a set of single nucleotide polymorphisms associated with type 2 diabetes mellitus. These associations, although they usually explain a relatively modest portion of disease risk, constitute proof of the principle underlying the genomewide approach to the elucidation of complex genetic traits. Up to now, allelic variants in about 10 loci have been confirmed to be associated with type 2 diabetes mellitus. One of them, a transcription factor, TCF7L2, has been replicated in several of the most recent whole genome association studies and fits very well with the adaptive hypothesis and concomitance of type 2 diabetes mellitus and obesity in East Asian, European, and West African populations, one of its variants displaying an association with body mass and concentration of hunger-satiety hormones including ghrelin and leptin in male subjects, compatible with selective evolutionary advantages through energy metabolism [19].

Even the abdominal-type obesity appears to be, at least in part, genetically determined, as we have demonstrated by association and linkage with tumor necrosis factor–α polymorphism impacting differentially in men and women [20]. There is clear evidence that genetic background is an important contributor in susceptibility to perinatal imprinting in genetically defined rodent models [21]. The identification

of these genetic determinants in humans is only now forthcoming. The first common polymorphism simultaneously determining birth weight and fasting glucose was discovered in the promoter of glucokinase gene, which has a considerable influence on birth weight when present in the mothers or their offspring [22]. It was the first gene to be reproducibly associated with fasting glucose and fetal growth [23,24]. A common polymorphism in peroxisome proliferator–activated receptor–γ is associated with insulin resistance in adulthood, but is dependent on low birth weight: only those with low birth weight and the polymorphism develop insulin resistance [25]. Fetal growth restriction has been described recently to be associated with a single nucleotide polymorphism in leptin receptor 8 among 40 candidate genes in 2 independent cohorts of black women [26]. In addition, a novel role has been demonstrated for the angiotensin-converting enzyme I/D genotype, which, independently of parent genotypes, determines the low birth weight of babies carrying the DD genotype. This genotype effect is independent of sex or socioeconomic status. Complex interactions between environmental and genetic factors result in apparent U-shaped relationships between birth weight and several components of the metabolic syndrome, evident even in well-nourished, full-term newborns of Western populations. Therefore, the search for causality between early-life impacts on later CVD development clearly requires the integration of knowledge of both environmental and genetic factors to design early strategies for prevention.

5. Epigenetics

The thrifty genotype hypothesis has generated continued attention over the years, and its validity and general applicability have been disputed by several authors. For example, it has been suggested that the hypothesis does not adequately explain the rapid changes in obesity and type 2 diabetes mellitus incidence in modern societies [27]. Some authors have argued that, during the short history of *Homo sapiens*, famines have not provided sufficient selective advantage for the penetration of a thrifty genotype in modern populations, whereas others have hypothesized that all human genotypes are thrifty and encode only small differences in energy efficiency. The high prevalence of type 2 diabetes mellitus can be considered a by-product of our biological incapacity to cope with modern affluent and sedentary lifestyles, with no consistent evidence to suggest that minority populations are especially genetically susceptible [28]. Even Neel reevaluated his evolutionary model 36 years later to broaden it to a more complex interplay between genetic and nongenetic factors. Rapid adjustment and optimization, at times necessary for survival, require a type of plasticity that the genome sequence cannot achieve. Without modifying the genomic backbone, epigenetic information enables its modulation in response to a given environment [29]. Under extreme conditions, such as famine, epigenetic information superimposed on the genetic network will enhance metabolic thrift [27]. Metabolic programming does not change the DNA sequence; but rather gene expression is altered by epigenetic modulation, such as DNA methylation, histone acetylation/methylation/phosphorylation/sumoylation patterning, and chromatin remodeling. The pattern of epigenetic information varies from cell type to cell type. Once established in a differentiated cell type, epigenetic signals are stably inherited through mitosis and are essential to maintain the correct gene expression profile within cells of that type during the organism's life [30]. Heritable effects induced by environmental factors have been documented in humans and rodents, some of which have been associated with epigenetic changes and span at least 2 generations. Deoxyribonucleic acid methylation may be one of the epigenetic modifications involved in response to environmental challenges. It is the best characterized epigenetic modification, is not universal, and has been confined to higher eukaryotic organisms. The fundamental role of DNA methylation is the regulation of gene expression. Methylation-mediated transcriptional silencing is essential in several developmentally important processes, including allele-specific gene expression (parental imprinting and X-chromosome inactivation). Gene silencing by DNA methylation also controls cell specificity of the gene expression profile. It has been suggested that dietary manipulation in utero could promote gene silencing by cytosine methylation of CpG-rich regions of metabolic genes, such as those implicated in energy acquisition, storage, and utilization. The promoter region of leptin is methylated in somatic tissues of humans and mice, displaying epigenetic variation [31,32].

A landmark study in rats described the role of epigenetic modifications of the glucocorticoid receptor gene in establishing the level of stress felt by adult animals [33], introduced through maternal behavior and, more recently, demonstrated to be retromodulated in adulthood [34]. Our capacity to adapt over millennia to a changing environment is perhaps best characterized by the accumulation of geoethnically diverse polymorphisms, all allowing for lactose-persistence alleles to persist to adulthood in societies dependent on domesticated animal milk production for survival, early in agricultural development. We can dispute the lack of capacity in human adaptation in a specific length of time by reminding ourselves of the acquisition of lactose persistence/tolerance (lactose intolerance developed after weaning being the wild phenotype). Lactose tolerance occurred in humans by the acquisition of mutations within the lactase gene early during the agricultural period (only more than 10,000 years ago) in relation to cattle domestication and following the path of human expansion to the North. This capacity to survive on milk is furthermore supported by

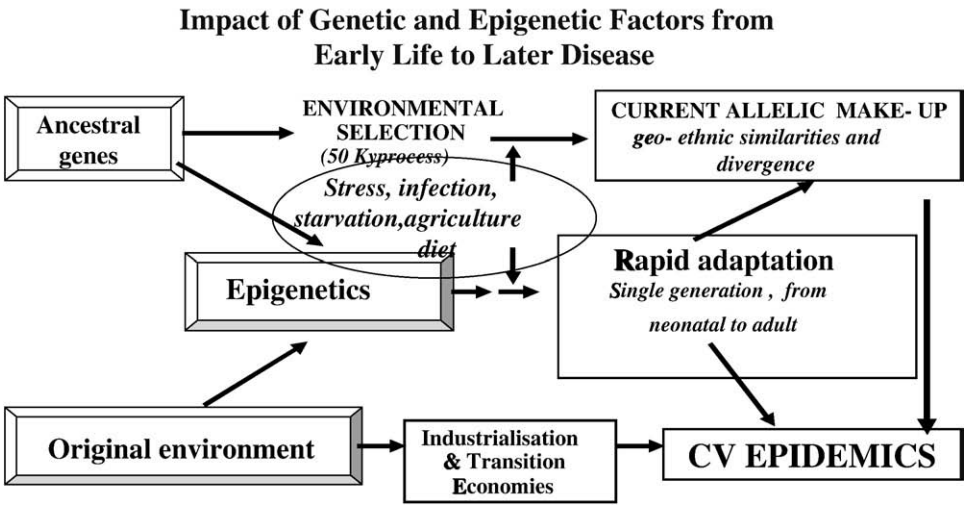

Fig. 1. Schematic representation of the impact of genetic and epigenetic determinants, from early life to later disease development. Ancestral genes and early environment interact from *Homo sapiens sapiens*, evolving over millennia by accumulating survival-favoring mutations and their expansion in various geoethnic groups to reach today's polymorphisms. Environmental challenges can also change within a generation, particularly over the developmental period, via epigenetic modulation, genomic function with potential impact on the later development of cardiovascular and other diseases.

different mutations in people separated by only 10000 years and is encountered even in Saudi Berbers who depend very much on camel milk [35].

6. Conclusion

The evolutionally acquired genomic susceptibilities and environmentally induced epigenomic modulations summarized above fashion our capacity to adapt to changing environments through periods of nutritional abundance and scarcity and of other environmental stress (Fig. 1). The consequences are of relevance to both individual and public health. We are fortunate that today's methodologies will allow us to continue to resolve these issues requiring an open-minded, integrative, and multidisciplinary approach. To ensure the healthiest development possible, knowledge of both "nature and nurture" is required [2].

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