Transgenerational Epigenetic Inheritance of Developmental Origins of Health and Disease

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1 Introduction

For the past few years, the national economy has been booming on people's living conditions, especially on the way of development. The incidence of some metabolic diseases like obesity has increased. At the same time, diseases like neurodegeneration and mental diseases are seriously threatening human health. The emergence of the developmental origins of health and disease theory provides a feasible means for disease prevention and treatment, and the relationship between the theory and transgenerational inheritance has attracted the attention and discussion of researchers.

2 Development History of DOHaD

In the 1970s, Forsdahl was the first to report that the risk of death which resulted from coronary heart disease has something to do with poverty and prosperity and indicated that a close relationship has been seen between permanent damage to the body caused by nutritional deficiency during pregnancy and such a phenomenon. Subsequently, studies launched by Barker and his colleagues showed that nutritional deficiency during pregnancy was closely related to the occurrence of cardiovascular risks, high blood pressure, abnormal blood fat, and central obesity along with

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disordered glucose metabolism in later generations [1]. Based on this research, the hypothesis of FOAD was used to portray the possible relationship between adult disease and fetal period. Further studies found that fetal growth restriction and postnatal growth patterns caused by an adverse intrauterine environment has significant effects on adult onset. Thus, the study of the origin of health and disease was formally introduced in 2003.

Currently, with modern medicine and some related disciplines growing rapidly beneath our eyes, DOHaD theory has been constantly improved, and harmful factors are unfolded before people's eyes gradually. Definitely, maternal pregnancy has a greater influence on the health and disease of one's offspring than paternal factors [2]. According to animal models and epigenetic theory, fathers also contribute to disease and health of the offspring [3]. However, people still have a shallow understanding of the impact of fathers on the health of their offspring. At the Latsis Symposium 2017 seminar, this issue was in depth discussed and much attention should be taken by the field of public health. Early-life exposure is mainly transmitted through maternal exposures or traits [4, 5].

3 Intergeneration Effect and Transgenerational Inheritance

3.1 Intergenerational Effect

Genetic information independent of DNA sequence, acknowledged as epigenetic data, tends to be inherited between adjacent generations [6, 7]. Through animal models, researchers call the complex information layer outside the DNA sequence epigenetic markers. This marker can be passed from parent to child through gametes for intergenerational inheritance [8]. Moreover, nutritional conditions during uterine development have a permanent impact on the subsequent development of the fetus, such as metabolic diseases mentioned above [9] (Table 1).

Although epidemiological studies and related animal model studies support the hypothesis of "thrifty phenotype," to date, most studies have focused on epigenetic effects between generations rather than on epigenetic effects represented by segregation. Studies have shown that exposure to pollutants, alcohol, tobacco, and other environments can affect the normal development of the fetus, and even the improper experiences of young children during their development may have a great impact on their mental health in adulthood [2, 9, 17].

Table 1 Examples of epigenetic intergenerational inheritance

Environmentally induced intergenerational inheritance	References
Paternally indeed transgenerational inheritance of susceptibility to diabetes in mammals (rats; prediabetes increases the susceptibility to diabetes in offspring)	[7]
Thee Gpr1/Zdbf2 locus provides new paradigms for transient and dynamic genomic imprinting in mammals (locus; paternal sDMR provides lifelong, paternal specificity)	[8]
Maternal exposures to persistent organic pollutants are associated with DNA methylation of thyroid hormone-related genes in placenta differently by infant sex (Korea mothers; placental epigenetic changes of key thyroid regulating genes)	[28]
A low DNA methylation epigenotype in lung squamous cell carcinoma and its association with idiopathic pulmonary fibrosis and poorer prognosis (patients with IPF; low-methylation lung SCC that significantly correlates with IPF shows unfavorable outcome)	[32]
DNA methylation links prenatal smoking exposure to later life health outcomes in offspring (the offspring of smokers during pregnancy; an increased risk of inflammatory bowel disease or schizophrenia)	[41]
Maternal and post-weaning high-fat diets produce distinct metabolic pathways within specific genomic contexts (male Sprague-Dawley rats; maternal and post-weaning HF exposure differentially affect the epigenome within specific genomic contexts)	[48]

3.2 Transgenerational Inheritance

It has been found that some of the epigenetic markers are essentially removable [10]; however, epigenetic modifications are not invariably eliminated thoroughly within generations [11, 12]. Reproductive cell reprogramming is an important stage of biological development for intergenerational inheritance. Sperms carries its genetic modification into the egg, and few times after fertilization, the epigenetic modification except for the imprinted region is removed [13, 14]. The ICM cells begin to differentiate, and the epigenetic modification is implanted. When primordial germ cells and somatic cells diverge, almost all of the epigenetic modifications, including imprinted regions, are removed together. Finally, epigenetic modifications are implanted during sperm development.

There are two threads for the strict transgenerational inheritance effects. First, in males, the F0 generation is exposed to specific toxins and nutrients that can induce epigenetic effects, and the second generation (F2 generation) may acquire epigenetic effects; second, while in females, the third generation (F3 generation) may acquire epigenetic effects ultimately. The reason is that the above exposure environment will affect the male and reproductive lines of F0 generation, and also affect the female and reproductive lines of F0 generation and F1 generation. Therefore, the epigenetic characteristics acquired by these generations are not truly segregated to represent epigenetic inheritance. This review screens and distinguishes intergenerational and transgenerational inheritance (Fig. 1).

Does the DOHaD theory have something to do with transgenerational inheritance? The answer is yes. Substantial experiments of animal models indicate that

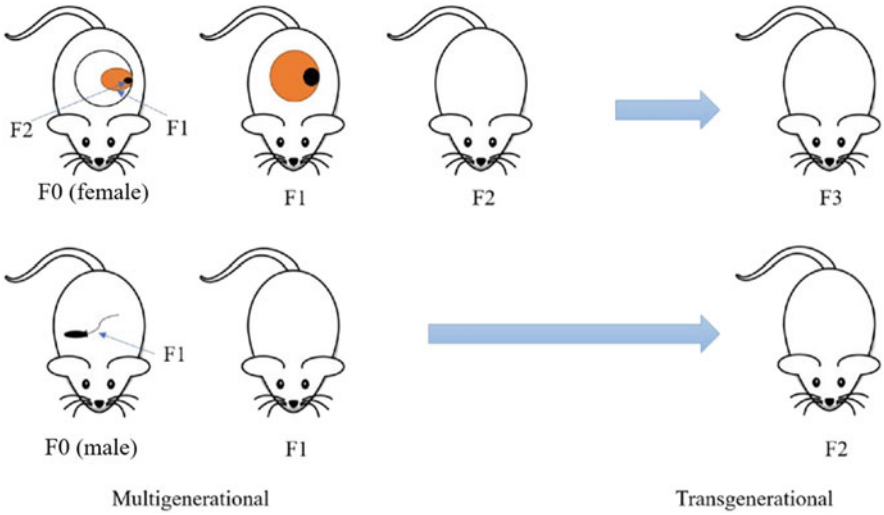

Fig. 1 Schematic of how the environmental exposure affects transgenerational inheritance. Strict transgenerational epigenetic inheritance, as shown in the figure, requires epigenetic characteristics acquired by F3 generations of female lines and F2 generations of male lines after exposure

DOHaD has transgenerational and multigenerational effects [15]. Morrison et al. [16] conducted a guinea pig model experiment and it is noteworthy that the F0 generation did not show the corresponding epigenetic characteristics, while the F2 and F3 generations showed the epigenetic characteristics. DDT has been shown to give impetus to transgenerational inheritance in adult diseased rats. Stephanie et al. exposed pregnant F0 female rats to DDT for a short time and then measured the incidence of some diseases in the subsequent F1, F2, and F3 generations. The finding was that in F2 generations, testicular diseases were more common in males than in adolescents, and in F3 generations, ovarian and kidney diseases increased [17]. Similarly, Anway and Skinner et al. [18, 19] used EDCs like vinclozolin to induce sperm epigenetic mutation to elucidate that epigenetic effects exist in the genesis and development of reproductive lines which may be related to transgenerational diseases.

But in the final analysis, the transgenerational genetic mechanism cannot be separated from the support of epigenetics, especially DNA methylation, histone modification, and the role of ncRNA [20] (Table 2).

Table 2 Examples of epigenetic transgenerational inheritance

Environmentally induced transgenerational inheritance	References
Correlation between altered DNA methylation of intergenic regions of ITPR3 and development of delayed cerebral ischemia in patients with subarachnoid hemorrhage (patients with SAH and DCI; higher levels of methylation intensity)	[10]
Stable inheritance of an acquired behavior in *Caenorhabditis elegans* (*C. elegans*: produce life-long olfactory imprints)	[13]
Primordial germ cell development and epigenetic reprogramming in mammals (rats; reveal the critical steps during PGC development)	[14]
Sperm epimutation biomarkers of obesity and pathologies following DDT-induced epigenetic transgenerational inheritance of disease (rats; inherited disease)	[17]
Transgenerational sperm DNA methylation epimutation developmental origins follow ancestral vinclozolin exposure (rats; developmental programming of the transgenerational epigenetic inheritance phenomenon occurs throughout the development of the germline)	[19]

4 Epigenetic Mechanism

4.1 What Is Epigenetic

In 1957, Conrad Waddington put forward the theory of "Waddington's epigenetic landscape" to clarify the concept of developmental biology. This theory has been processed and perfected by later generations, thus becoming epigenetics that we are now familiar with [21]. This theory implies that genetic changes occur when the nucleotide sequence of a gene does not change [22–24]. The term "epigenetics" does not refer to an additional layer above a gene; rather it is a process of gene development in which genes are expressed by different choices to gradually construct individuals [25]. Epigenetics has been used for a proper explanation of the difficult and incomprehensible problems of biology. Also it can be used to explain a long-standing mystery. By revealing how gene expression is regulated, we can better understand how genetic and non-genetic factors coordinate to determine our characteristics [26, 27]. The non-genetic factors are mainly regulated by a series of epigenetic markers. Currently, many researchers associate epigenetics with many complex diseases, such as methylation in DNA as well as RNA analysis in peripheral blood cells of patients with some diseases [28] and have made some breakthroughs, which provide a new perspective for looking at aging and various diseases [29]. Of course, the explanation of the DOHaD theory is inseparable from the study of epigenetics. At present, epigenetic studies have been carried out in areas such as neurodegeneration, cancer, metabolic diseases, and allergic diseases, which have renewed understanding and insights into the occurrence and treatment of diseases [30–35].

Epigenetic mechanisms mainly include DNA methylation, regulation of ncRNA, and histone modification. These mechanisms make a great difference in DOHaD [36–39].

4.2 DNA Methylation

Enzymes that produce, distinguish, or clear DNA methylation are classified into three categories: writers, erasers, and readers. The writer catalyzes methyl addition to cytosine residues, eraser modifies and removes methyl, and the reader recognizes and binds to methyl to affect gene output. It is through these mechanisms that DNA methylation affects DOHaD [40–42].

DNMT1, DNMT3A, and DNMT3B can directly add methyl to DNA in the DNMT (methyltransferase) family that compiles DNA methylation [43]. DNMT1 has its particularity that tends to methylate semi-methylated DNA in the process of DNA replication. DNMT1 methylate, according to the pre-replication methylation mode, can repair methylation, thus maintaining the stability of methylation of a gene [44, 45]. However, it is still unclear how methyltransferases target specific gene loci.

DNA methylation reduces the expression of some gene fragments by blocking the combination of transcriptional activators. It is worth investigating thoroughly that DNA methylation can be recognized by three family proteins: MBD protein, UHRF protein, and zinc finger protein. When methylation is recognized by these proteins, gene transcription is suppressed [46, 47].

4.3 Histone Modification

Modification of histone can be multifarious, especially when propionylation, methylation, and acetylation are included. Abnormal histone modification can lead to various pathological changes [48].

The interaction of DNA methylation and histone modification on mitochondria results in genomic imprinting. It is due to the epigenetic modification of the allele derived from a parent or its chromosome that the two alleles from different parents express differently in progeny cells [49–51] (Fig. 2).

4.4 Noncoding RNA

Through improved methodologies, researchers have found that parts of the genome that do not encode proteins do transcribe a lot, but are initially misunderstood as "transcriptional that has a firm foothold beside proteins." However, their different roles cannot be ignored [52–54]. Studies have confirmed that ncRNAs can silence multiple genes by binding to chromatin and recruiting modification elements. This counts a lot in the process of random inactivation of the X chromosome and can also be seen in DNA damage repair. An increasing number of studies have found that ncRNAs function by forming nucleic acid-protein interactions [55, 56].

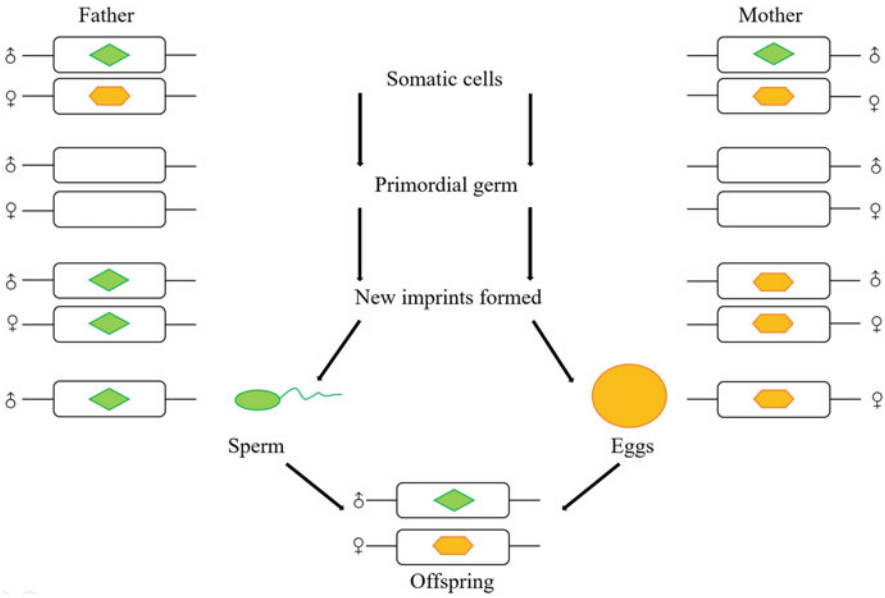

Fig. 2 The inheritable process of imprinted genes. The figure shows the reprogramming during germ cell development. A large number of imprinted genes controlled by epigenetics can resist reprogramming of fertilized eggs, but cannot resist reprogramming during germ cell development

4.5 Other Mechanisms

These three mechanisms are the most widely studied. Besides, researchers continue to seek breakthroughs from other perspectives. Maternal effects, dormant transposon activation, and some other mechanisms [57, 58] are not the points of this review. Last but not least, many diseases are not caused unilaterally by one mechanism, but by the abnormal occurrence of multiple mechanisms.

5 Development Prospects and Clinical Significance

In the past 50 years, modern medicine has developed by leaps and bounds. However, some non-communicable chronic diseases are still a thorny problem. As a result, the DOHaD theory has appealed to many people's eyes. Researchers in the field of public health around the world are trying to curb the development of diseases from the source. Many cases have confirmed that malnutrition during pregnancy can lead to a series of metabolic disorders such as diabetes and abdominal obesity in offspring [59]. In most countries that are developing or hard to develop themselves, the general level of economic development is not high, accompanied by material shortage and other adverse conditions, which has caused indelible harm to pregnant children, even

through epigenetic mechanisms to the next generation [60]. Due to global resources distributing unevenly, the environmental exposure of young children during embryonic and early development varies from region to region [61]. Pertinent departments try their best to adapt to local conditions and analyze specific problems to improve the living standards of local inhabitants, the youth accounting for a large proportion particularly along with women in pregnancy. At the same time, children around the world should be educated about the DOHaD theory and improve their understanding of some important concepts. Only by understanding the role of early experience in promoting adult diseases can children improve their awareness of prevention and do a good job in preventing some chronic diseases [62, 63].

We should monitor these diseases with the help of large clinical data to facilitate further research [64]. Embryonic and early childhood development are "windows of opportunity" for intervention from the source of disease. On one hand, continuous intervention in the living environment of pregnant women and children during this period can help to prevent diseases [65]; on the other hand, by analyzing the environmental exposure of fetuses and young children in early stage, we can predict the risk of related diseases and be able to timely prevent and control them [66].

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