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Developmental Origins of Health and Disease: A Paradigm for Understanding Disease Etiology and Prevention

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Abstract

Purpose of Review—While diseases may appear clinically throughout the lifespan, it is clear that many diseases have origins during development. Altered nutrition, as well as exposure to environmental chemicals, drugs, infections, or stress during specific times of development can lead to functional changes in tissues, predisposing those tissues to diseases that manifest later in life. This review will focus on the role of altered nutrition and exposures to environmental chemicals during development in the role of disease/dysfunctions.

Recent Findings—Effects of altered nutrition or exposure to environmental chemicals during development are likely due to altered programming of epigenetic marks which persist across the lifespan. Indeed some changes can be transmitted to future generations.

Summary—Evidence in support of the DOHaD paradigm is sufficiently robust and repeatable across species including humans, suggesting a need for greater emphasis in the clinical area. Because of these data, obesity, diabetes, cardiovascular morbidity, and neuropsychiatric diseases can all be considered pediatric diseases. Disease prevention must start with improved nutrition and reduced exposures to environmental chemicals during development.

Keywords

developmental origins of health and disease (DOHaD); epigenetic program; transgenerational inheritance; environmental chemicals; nutrition

Introduction

A 60 year old man is diagnosed with Parkinson's, a 50 year old women has breast cancer, a 30 year old man is obese with metabolic syndrome, a 20 year old man is infertile, a 9 year old girl has asthma, and a 6 yr. old boy has learning disabilities. With all of these different diseases arising at various times across the lifespan, what could they have in common? The

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answer is not found in genetics; although there is a genetic component to these diseases, mutations and polymorphisms likely account for only small and variable risk. Instead, the common link between all these non-communicable conditions is that they likely originated during early development as the result of environmental influences: altered nutrition, stress, drugs, infections or exposure to environmental chemicals. This review will provide an overview of the developmental origins of health and disease, as well as focus on the latest data showing transgenerational transmission of disease susceptibility.

Altered Nutrition during Development Influences Disease Risk across the Lifespan

The link between early life environmental factors and later life diseases was developed by David Barker, who in the mid-1980s showed that starvation of pregnant women during the Dutch 'hunger winter' of the second world war correlated with increased risk of cardiovascular and metabolic diseases in their offspring at adulthood [1]. Thus, the concept that poor nutrition during organ development could lead to increased risk of disease later in life was originally called the Barker Hypothesis, then the Fetal Origin of Adult Disease, and now the Developmental Origins of Health and Disease (DOHaD). While the original focus was on how fetal malnutrition contributes to adult hypertension, obesity and insulin resistance, newer studies have identified other diseases that can result from fetal over- or under-nutrition including immunological, mental health, and reproductive diseases [2-5].

Linking Environmental Exposures during Development to Increased Disease Risk across the Lifespan

Work exploring the link between exposures to certain chemicals and drugs during early development and disease risk across the lifespan developed independently of the work on fetal malnutrition. The strongest data suggesting a link between developmental chemical exposures and later life diseases include smoking [6], lead, methyl mercury [7] and diethylstilbestrol (DES), a pharmaceutical estrogen [8]. A comprehensive literature search identified 343 published epidemiology studies (through mid-2013) which suggested associations between developmental chemical exposures and later life diseases; more than 180 studies assessed the linkage between an environmental chemical exposure and some aspect of neurodevelopment including early life neurobehavioral and/or learning disabilities or IQ loss (Heindel, unpublished). For example, in 2011, three separate labs identified associations between prenatal exposures to organophosphate pesticides and altered IQ and cognitive development in separate cohorts of children[9-11].

Animal studies have also provided important information showing that developmental exposures to environmental chemicals can induce diseases in later life; many of the diseases implicated in these animal studies have been increasing in human populations over recent decades and affect a large proportion of the population including obesity, neurodevelopmental diseases/dysfunctions, asthma and immune dysfunctions [12, 13]. Animal studies also show causal relationships between developmental chemical exposures and diseases that have not been examined in human studies due to the long lag time between

exposures and disease onset such as breast and prostate cancer, neurodegenerative diseases, cardiovascular diseases and reproductive conditions including endometriosis, and uterine fibroids[13-15].

Similarities Between Different Developmental Disturbances and Disease Risk

There are many features common to environmental influences during development including:

- There are specific sensitive windows of exposure leading to time- and tissue-specific effects. In general, increased sensitivity is noted during the time a specific tissue is forming which can occur *in utero* or extends to the first years of life depending on the tissue.
- The effects do not result in birth defects or malformations which are apparent at birth. Instead, subtle functional changes include altered gene expression (which can lead to altered proteins), altered cell numbers, and altered metabolism.
- These functional changes increase risk of disease/dysfunction, long after the transient environmental perturbation during development, with a latency period of months to years to decades.
- The result of these functional changes can lead to increased incidence of a disease or dysfunction, an earlier onset of the disease, or an increased severity.
- The effect may depend on genetic background and can be gender specific.
- Some effects can be transmitted via the germ line to subsequent generations resulting in multigenerational and transgenerational effects.

Since both under- or over-nutrition and environmental chemical exposures have so much in common and likely occur together, it is imperative that all data are integrated to gain a real picture of the effect of altered developmental programming and disease outcomes across the lifespan.

Mechanistic Understanding of How Developmental Environmental Stressors Contribute to Adult Diseases

The increased sensitivity of the developmental period is thought to be a reflection of the plasticity of developing organisms. During early embryogenesis, pluripotent cells differentiate into all the cells and tissues of the body; this process is under the control of hormones and other signaling molecules such as growth factors. Changes in stress, nutrition, or exposure to infections, drugs or a variety of environmental chemicals can alter the orchestrated process of cell differentiation.

Furthermore, environmental factors can influence the epigenome – the non-coding alterations that affect DNA and thus influence gene expression – which can predispose these cells and tissues to disease/dysfunction across the lifespan. Two well understood epigenetic

mechanisms are DNA methylation near gene promoter regions and histone modifications. These modifications can control gene expression in an integrated and coordinated manner. For example, histone modifications and the recruitment of DNA regulatory proteins can lead to changes in transcription, but only if the gene promoter region is not methylated and is therefore open to transcription factor binding. This cross talk is mediated by proteins that decipher the regulatory information that is encoded in the DNA methylation and histone marks [16]. The developmental periods encompassing gestation and the first few years of life are uniquely sensitive to environmental perturbations at least partly because of the sensitivity of epigenetic 'marks' to environmental influences during tissue differentiation. Once tissues are formed, the tissue epigenome, while somewhat dynamic, is relatively stable and therefore much less sensitive to environmental influences. Thus each tissue will have a specific time – a 'critical window' – when it is highly sensitive to environmental influences on the epigenome. Some tissues fully develop before birth, whereas others like the brain, immune and metabolic systems continue to develop into childhood.

While a causal link between epigenetic changes and the increased susceptibility to disease later in life has not been established, epigenetics is a strong plausible molecular mechanism that links genes, environment and the susceptibility to disease[17-20]. Indeed, supplementation or restriction of the maternal diet with dietary factors can alter epigenetic patterns in offspring[21, 22]. A large number of tissue-specific differentially methylated sites were observed in livers of mice exposed to nutritional stress during development [23]. Similarly, epigenetic alterations were observed in the prostate after neonatal exposure to bisphenol A [24]. There is now a considerable literature demonstrating epigenetic changes that persist later in life from altered nutrition, stress or environmental chemicals during development; these epigenetic changes may serve as biomarkers of increased disease susceptibility.

Linking Developmental Exposures to Environmental Stressors to Diseases across Generations

One of the more fascinating and significant recent findings related to the DOHaD paradigm is that disease risk can be transmitted across generations. Most of this evidence has been generated in animal models. Transmission of disease risk from F0 (mother) to F1 (offspring) or F2 (grandchildren) is considered mutigenerational, and has significant implications for the transmission of diseases in humans. If the observed effects are also apparent in the F3 generation, then they cannot be due to direct effects of the environmental stressor as the F3 individuals were never exposed to the compound at any time; these effects are likely to be permanent and transmitted further down the ancestral tree. Effects transmitted to the F3 generation or beyond are called transgenerational.

The mechanisms underlying transgenerational inheritance, while proposed to involve transmission of epigenetic information, is far from understood and likely involves other unidentified factors[25-29]. When primordial germ cells are developing, they are depleted of all epigenetic marks, allowing them to become pluripotent cells; epigenetic marks are added back in a time- and sex-specific manner. Thus transmission of epigenetic information across generations is only possible if the epigenetic marks are not erased during germ cell reprogramming, which does appear to be the case for at least some methyl groups [30].

Environmental chemicals administered during precise time periods of fetal development generate phenotypes in animal models, not only in the parental generation, but in the children, and sometimes in the grandchildren [31]. Some diseases or gene expression changes can even be found in the F3 generation (great-grandchildren) and beyond, presumably resulting from chemical exposures that affect DNA loci that escape reprogramming during gametogenesis[32-34]. Changes in the F3 generation sperm epigenome have been identified after developmental exposure to the fungicide vinclozolin[35], dioxin [36], the insecticide DDT [37],a hydrocarbon mixture (jet fuel JP-8) [38] and a pesticide/insect repellent mixture (permethrin and DEET) [39]. Transgenerational effects on the incidence of ovarian diseases and testicular dysfunction have also been reported [40]. Other transgenerational effects that have been linked to chemical exposures include: 1) effects of BPA on social behavioral changes in the F4 generation via epigenetic changes in imprinted genes [41]; 2) effects of the fungicide tributyl tin (TBT) on adipose depot weight, adipocyte size, mesenchymal cell fate, and fatty liver in the F1, F2 and F3 generations [34]; 3) inheritance of obesity from exposure to DDT, a mixture of BPA and the plasticizer, Di(2-ethylhexyl)phthalate (DEHP), and jet fuel JP-8 [36-38]. Collectively, these results demonstrate that the effects of early-life exposures to some environmental chemicals can be permanent and transgenerational, increasing the risk of future generations to develop diseases including obesity, some cancers and reproductive dysfunctions [42]. The mechanism(s) for these effects are still unclear.

Intrauterine under-nutrition can also induce epigenetic changes in the F1 germ line which are linked to alterations in the F2 generation and increased risk of metabolic syndrome[43-45]. Several groups found effects on the F2 generation when the pregnant dam (F0) was exposed to low protein diets, calorie restriction, high fat diets, or when gestational diabetes was induced; effects were observed on glucose tolerance, blood pressure/vascular dysfunction, body weight, insulin resistance, immune dysfunction, reproduction and neurological dysfunctions [25, 26, 46]. While the majority of these studies showed transmission of effects through the maternal line, some effects were noted when only the father was exposed to the stressor[26]. Most of these studies did not show transmission to the F3 generation, indicating a lack of true transgenerational inheritance, however a few studies reported effects of high fat or low protein diets on body weight, glucose tolerance, insulin secretion and pancreatic beta cell mass in the F3 generation [26] similar to what has been observed after environmental chemical exposures.

Conclusion

Evidence in support of the DOHaD paradigm is sufficiently robust and repeatable across species including humans, suggesting a need for greater emphasis in the clinical area. Because of these data, obesity, diabetes, cardiovascular morbidity, and neurodegenerative diseases can all be considered pediatric diseases: not because they show up in children but because they originate during development. The importance to pediatricians is that the sensitive developmental window covers not just in utero exposures but also early childhood. In some tissues, like brain and immune system, the developmental period is extended through puberty. Thus, for many diseases, it is clear that a new focus on the timing of disease prevention is needed. Early interventions during the prenatal period and the first few postnatal years, the time when tissues are forming and the epigenetic system is most

sensitive to environmental insults, have the potential to lead to improved lifelong health. The targets for reducing risk of disease across the lifespan and generations are the pregnant mother and their infants and young children through puberty. There are also recent data showing that exposures of the father can affect sperm epigenetics [47] suggesting the possibility of paternal effects on disease susceptibility. The clinician is ultimately at the center of the battle to prevent diseases that occur across the lifespan and indeed even across generations.

The Endocrine Society [48, 49], the American College of Obstetricians [50], the American Society of Reproductive Medicine, and the Royal College of Obstetricians and Gynaecologists [51], the European Society for Paediatric Endocrinology and the US Pediatric Endocrine Society [52] and other scientific groups [13] have put forward statements calling for action on environmental chemicals due to the sensitivity of developing individuals and the resulting increased disease risk across the lifespan. They also call for a focus on disease prevention. Improving/optimizing nutrition, reducing stress, drugs, infections and exposure to environmental chemicals during pregnancy and early childhood offer an opportunity to reduce the risk of many communicable diseases

Finally, it should be noted that while development is a sensitive period for the effects of environmental influences on disease risk, there are likely other periods during the lifespan that are important. These may include other periods with major changes in hormones and growth such as the period of infancy to childhood, puberty, peri-menopause, pregnancy and aging [16]. It is not clear how important each of these transition periods are to disease risk or how they might interact.

As noted by Silver and Singer [53], investing in child development is the foundation for improved health, economic and social outcomes. The embracement of the DOHaD paradigm provides an opportunity for both patients and physicians to prevent diseases and intervene to lessen their impact, and to take action years before disease onset is evident.

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* of special interest

** of outstanding interest

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Key Points

- Evidence in support of the DOHaD paradigm is sufficiently robust and repeatable across species including humans, suggesting a need for greater emphasis in the clinical area.
- Environmental chemicals exposures or nutritional stress during precise time periods of fetal development, in some cases, generate phenotypes in animal models, not only in the parental generation, but in the children, and sometimes in the grandchildren and great-grandchildren.
- Early interventions during the prenatal period and the first few postnatal years, the time when tissues are forming and the epigenetic system is most sensitive to environmental insults, have the potential to lead to improved lifelong health.