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Review

Fetal Programming: Lung Health and Disease

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Abstract

Fetal programming is a mechanism whereby stimuli acting on the developing fetus influence the development of the fetus in a way that may set the stage for adult health and disease. These stimuli may be environmental, such as maternal smoking; metabolic, such as the maternal diet and nutrition; or endocrine, such as diabetes or stress, and may extend over several generations. The endocrine system influences fetal programming with effects of insulin, thyroid hormones, and glucocorticoid hormones. Epigenetic information may be modified by DNA methylation, histone modifications, and micro RNAs due to environmental exposures.

In this review, we describe the normal development of the lungs and the major factors that may influence lung growth and development with the potential for sequelae into adult life.

KEYWORDS: Fetal programming, epigenetics, environment, exposure
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INTRODUCTION

Fetal programming, first described by David Barker in the 1990s,[1] can be defined as permanent changes in metabolism, organ structure, and physiological processes that may be carried into adulthood as a result of various stimuli acting on the fetus during critical periods of growth. Critical or sensitive periods differ among different cell and organ groups; therefore insults at different stages of development may have different consequences.[2] These changes determine the susceptibility to, or protection from, various adult diseases.[3,4] The concept of fetal programming followed the observation by Barker[5] that plasma fibrinogen levels, impaired glucose tolerance, and systolic blood pressure in adulthood are related to birthweight or weight at 1-year of age. He concluded that intrauterine or early-life growth restriction is a risk factor for the prevalence of, and mortality from, cardiovascular disease. Critical to this finding is that it helps to explain why risk factors in adult life correlate poorly with cardiovascular diseases.[5]

Fetal lung development begins with tracheal separation at the third week of gestation in the embryonic period, and continues after birth with continued development of mature alveoli. In between these periods, there are pseudoglandular, canalicular, and saccular periods characterized by various levels of airway branching development and pulmonary vascular development. Surfactant production starts at the 24th week of gestation resulting in a major change in the lung physiology. Any stimulus that influences these developmental stages has the potential to have long-term effects on lung health.[6]

ENDOCRINE MECHANISMS UNDERLYING FETAL PROGRAMMING

Fetal hormones can originate from different sources: the fetus itself can secrete hormones from the pancreas, thyroid, pituitary, and adrenal glands; uteroplacental hormones such as steroids and maternal lipophilic hormones can reach the fetal circulation from the mother through transplacental diffusion and the uterine circulation.[7]

INSULIN AND INSULIN-LIKE GROWTH FACTORS

Insulin has a significant influence on fetal growth. The fetus of a mother with diabetes secretes excessive insulin and insulin-like-growth factors (IGF)—due to the increased levels of glucose, lipid, and amino acids—that pass to the fetal circulation.[4] Insulin increases proliferation and calcium response of primary human airway smooth muscle cells, promotes collagen release, and activates B-catenin that induces epithelial–mesenchymal transition and fibrosis in mice. The relevance of these observations to the human fetus is unclear but illustrates the potential of insulin to affect human fetal development.[8]

IGF are important regulators of somatic growth. Similarly, they are involved in alveolarization that is also regulated by many other growth factors including platelet-derived vascular endothelial and fibroblast growth factors. IGF-I and IGF-II share a common receptor called IGF-IR. IGF-I is essential for synthesis of elastin and collagen, which are required for alveolar development. In an experimental rat model, injection of neutralizing IGF-I receptors (IGF-IR) during early days of life resulted in decreased lung weight and lung tissue fraction as well as disrupted alveolar formation. Moreover, there was

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a decrease in procollagen and elastin fiber density in these rats.[9,10] The consequence of this is significant lung hypoplasia, thickened mesenchyme, and maturational delay.[10,11]

Moreover, cell proliferation and apoptosis increase while cell differentiation decreases in lung tissues of IGF-IR knock-out animal models, leading to significant lung hypoplasia, thickened mesenchyme, and maturational delay.[11] IGF-I, IGF-II, and IGF-I receptor mRNA are expressed as early as fourth week of gestation. Application of IGF-1R-blocking antibodies to human lung explants resulted in endothelial cell loss as well as morphological changes, indicating the role of this receptor in vasculogenesis and angiogenesis during this early period of gestation.[12]

Exposure to tobacco smoke also reduces fetal lung weight and function in rats. This IGF-1 dysregulation has been proposed to influence the offspring's response to environmental insults that result in respiratory disorders.[13]

Collectively, these findings underline the role of insulin and IGFs in lung growth and maturation besides general somatic growth.

THYROID HORMONES

The thyroid hormones play an important role in the neural development of the fetus, and are transferred from the mother until their production starts in the fetus early in the second trimester.[14] While they do not seem to influence lung growth until the saccular period, they do affect postnatal alveolar growth and mRNA expression of cellular surfactant protein. Thus, thyroid hormone deficiency does not have a negative impact on intrauterine lung morphogenesis but influences postnatal alveologenesis.[15]

Thyroid transcription factor-1 (TTF-1) expressed in epithelial cells of the respiratory tract from 11 weeks gestation plays a role in lung morphogenesis as well as in the regulation of type II pneumocyte maturation and surfactant metabolism.[16,17] Lack of function of the TTF-1gene leads to a decrease in lung mass and hypoplasia, arrested terminal maturation of type II cells, and decrease in vasculogenesis and VEGF expression, finally resulting in incomplete differentiation of peripheral bronchiole and acinar cells while lobulation and early branching are normal.[17]

GLUCOCORTICOIDS

Glucocorticoid levels in the fetus increase in the 35th week of gestation in the human fetus. This period coincides with important events in fetal lung development, such as pulmonary mesenchyme thinning, alveolar duct increase, and maturation of the surfactant system. All these changes prepare the lung for gas exchange.[6]

Glucocorticoid hormone receptors are nuclear hormone receptors and expressed in many fetal tissues as well as placenta.[2] Nuclear hormone receptors are unique in their capacity to transform the chemical signal directly into a transcription modification by binding to the nuclear DNA.[18] Therefore, the maturation-enhancing properties of glucocorticoids are observed in many vital tissues such as the lung and central nervous system. This widespread network of receptors explains the effect of endogenous and exogenous glucocorticoid exposure on fetal development and adult health.[2]

EPIGENETICS

Epigenetics is a heritable change in the expression of the genetic material or phenotype without a change in the gene sequence, and can occur at any age.[19] Both genetic information and environmental exposures have the capacity to modify the epigenetic information mainly by DNA methylation, histone modifications, and microRNAs. DNA methylation is the covalent modification of the cytosine nucleotide that usually leads to silencing of the gene, and that is carried through cell division.[20] DNA methylation is the transfer of a methyl group to 5' position of the cytosine ring in CpG dinucleotides, and it has a regulatory role in the transcription of the region by inhibiting binding of the transcription proteins. Histone modifications involve post-translational covalent modifications by transfer of molecules, mostly acetyl, to the N-terminal of the histone protein.[21,22]

These mechanisms are usually activated by environmental stimuli such as maternal smoking, air pollution, or dietary ingredients, and can lead to change in expression of the genetic material and may be passed on to the next generations. Epigenetic changes such as DNA methylation can occur at any age, but intrauterine and early fetal development are the most vulnerable periods due to rapid division and replication of cells.[21,22]

Maternal nutrition and smoking during pregnancy are 2 factors that are perhaps the most important in determining the DNA methylation pattern of infants. Methionine, choline, betaine, and cofactors such as folate are examples of nutritional factors in the maternal blood that can influence DNA methylation in the fetus, some by influencing the synthesis of S-adenosylmethionine that is the active precursor for DNA synthesis.[20,23] Apart from dietary amino acids, dietary fat content may also change DNA methylation patterns.[23] Moreover, maternal smoking can affect the methylation pattern of epigenome-wide genes associated with asthma. Epigenome-wide analysis of DNA methylation in smoke-exposed fetuses revealed a change in methylation pattern of the CpG sites, especially in the PKP3, ANKRD33B, CNTD2, and DPP10 genes. These genes have been associated with asthma, and the above described epigenetic mechanism may be one of the reasons for increased lung diseases in children exposed to in-utero smoking.[24]

MAIN POINTS

- Intrauterine and early infancy events can permanently alter many organs, leading to increased risk of adult diseases.
- Mechanisms of fetal programing include epigenetic modifications.
- Prenatal events and exposures need to be considered for prevention of adult chronic diseases.

It has been shown that maternal smoking is associated with higher wheezing and lower lung functions in the offspring. One of the mechanisms underlying this is proposed to be the oxidant stress. Vitamin C supplementation was shown to reverse the effect of maternal smoking on the lung function of the offspring. DNA methylation has also been shown to be responsible for the effect on lung function, and vitamin C supplementation during pregnancy in mothers who smoked prevented this methylation change associated with smoking.[25]

Persistent organic pollutants are chemicals such as pesticides that are used in many different products, especially foods. These chemicals are endocrine-disrupting, and exposure during pregnancy leads to unwanted consequences on maternal hormones. They change the methylation pattern of many placental genes—resulting in alterations of fetal metabolism and growth.[26]

Oxidative stress associated with preeclampsia leads to hypermethylation of histone proteins in fetal endothelial cells and thus histone-related post-transcriptional modification in fetal endothelial cells.[27] Moreover, there is an alteration of expression patterns of fetal microRNAs related to genes involved in metabolic pathways.[28] These examples suggest that epigenetic mechanisms underlie the fetal programming associated with maternal preeclampsia and obesity.[27,28]

METABOLIC AND NUTRITIONAL FACTORS OF FETAL PROGRAMMING

Maternal diabetes influences fetal growth by mechanisms mediated by insulin and IGFs. In animal models of mild diabetes, insulin and IGF levels have a greater effect on the fetus than on the mother.[11] Maternal diabetes is one of the gestational risk factors for lung disease after birth, because maternal hyperglycemia and concurrent fetal hyperinsulinemia lead to decreased surfactant protein and phosphatidylglycerol expression, eventually disrupting surfactant composition. Maternal diabetes is also associated with fetal hypoxia and disturbances in immunological responses that increase the risk of wheezing and asthma in childhood.[6] Moreover, increased free radicals and the related oxidative damage may be one of the mechanisms that underlie fetal programming for future diseases.[4]

Maternal nutrition is one of the major intrauterine risk factors that lead to changes in endocrine metabolism and growth of the fetus through modifications in fetal and placental hormone responses. In acute fetal undernutrition, cortisol levels increase while insulin and growth hormone levels decrease; if the undernutrition is prolonged, fetal growth is retarded in an attempt to improve viability by decreasing metabolic rate. However, this attempt, which is required in the fetal period, is carried into the adult period, resulting in increased glucose storage and insulin resistance.[5]

The consistency of maternal diet during pregnancy also influences postnatal allergy patterns in the offspring. A cohort study of 1002 pregnant women in Japan found that a western diet rich in processed meat, vegetable oil, and white vegetables protected against childhood wheezing compared to a diet rich in green vegetables and fish, and to a Japanese diet that is mainly rice and fish. This unexpected relationship could not be demonstrated for eczema.[29] On the other hand, another study demonstrated that high intake of eicosapentaenoic acid and docosahexaenoic acid decreased risk of preschool wheeze in children around 2 years old.[30]

Vitamin D is one of the hormones that has been extensively investigated to explore its role in allergic diseases and asthma. Maternal serum vitamin D levels in late gestation were not found to be related to asthma or allergic rhinitis.[31] However, higher neonatal vitamin D levels during the first week of life reduce the risk of developing asthma before 10 years age.[32]

In the study by McEvoy and colleagues[33] involving women who were unable to stop smoking during their pregnancy, vitamin C supplementation initiated during 13-23 weeks of gestation significantly improved lung function, specifically forced expiratory flow$_{50}$ (FEF$_{50}$) and FEF$_{25-75}$ of the infant at 3 months of age. Moreover, the infants who received vitamin C supplementation had lower risk of wheezing during the first year of life.[34,35] This important study underscored the importance of vitamin C during fetal development, and the small cost of augmenting vitamin C levels to correct the effects of maternal smoking.

Maternal overnutrition is as problematic as undernutrition in terms of fetal programming, and also influences lung development. Maternal overnutrition leads to depletion of carnitine molecules and consequently compromised mitochondrial metabolism. Carnitine has been proposed to promote surfactant phospholipid development.[36] Maternal obesity influences overall development of the fetus through many different mechanisms involving glucose, insulin, and leptin. There is activation of the renin–angiotensin system, increasing the levels of angiotensin II which is mitogenic for lung fibroblasts. Moreover, angiotensin receptors AT1 and AT2 are involved in interstitial pneumonia and lung fibrosis. Therefore, alterations in the renin–angiotensin system due to maternal overnutrition inhibit lung growth and transition to gas-exchange period in the fetus.[37] These findings have significant impact on public health, considering the high prevalence of obesity.

Depending on the organ development timeline, changes soon after birth may also influence lung development in adulthood. Low birthweight is associated with decreased spirometric and plethysmographic values in adulthood. Spirometry and body plethysmography at age 32 years showed that infants with low birthweights had lower FEV1, FVC, total lung capacity, and functional residual capacity, compared to infants with normal weight, supporting the finding that delayed intrauterine growth has long term consequences on lung development.[37]

EARLY ENVIRONMENTAL EXPOSURES AND FETAL PROGRAMMING

Maternal smoking during pregnancy increases the risk of many diseases in the infant. Fetal nicotine concentrations reach levels higher than those in the mother due to the immaturity of the metabolizing enzymes. Thus, fetal cells are exposed to the toxic effects of nicotine, such as genetic

instability, for a longer duration. Moreover, nicotine exposure leads to an increase in reactive oxygen radicals, toxic to nuclear and mitochondrial DNA.[2]

Some of the first important information on the permanent influence of environmental exposures during fetal and immediate postnatal period on airway development came from the European Community Respiratory Health Survey which had information on more than 15 000 people from different regions of Europe. Parental smoking was associated with poorer lung function tests and more common respiratory symptoms in adulthood. Moreover, they found a dose–response relationship between the number of parents smoking and respiratory symptoms. The results of the study demonstrated that males were more vulnerable to the effects of environmental tobacco smoke exposure during early childhood, whereas females were more vulnerable to intrauterine exposure, thus leading to the conclusion that age at exposure leads to different consequences in the 2 sexes.[38] Similarly, results of the Tucson Children's Respiratory Health Study demonstrated that young adults who smoke experience an early accelerated decline in lung function, specifically prebronchodilator Fev1/FVC ratios, if their parents had been smokers.[39] The Medical Research Council National Survey of Health and Development, which is a nationally representative cohort that started with 5362 infants in 1946, showed that exposure to tobacco smoke during adolescence or adulthood increases the negative impact of early-life exposures. Individuals who do not smoke have a chance of decreasing the outcomes of early-life exposures, but the ones who smoke lose this chance.[40] These findings are important to demonstrate that early-life exposures not only influence adult outcomes themselves but also modify the vulnerability of the individual to later exposures.

Exposure not only to tobacco smoke but also to traffic-related air pollution has negative impact on the later development of fetus. A study from Japan demonstrated that offspring of pregnant women who live close to major roads, especially if within 50 meters, are more prone to be diagnosed with asthma or atopic dermatitis during the first 2 years of life.[41] Similar results were found in a study that assessed the relationship between living close to major roads and allergic diseases such as allergic rhinitis or asthma at age 6 years, in Munich.[42]

CONCLUSION

A wide variety of intrauterine and early infancy events can permanently alter the structure and function of many organs, and increase the risk for adult diseases, including but not limited to cancer. Fetal programing constitutes the various mechanisms like epigenetic modifications, that lead to adult diseases as a result of early-life exposures. This concept has shifted the idea for preventing chronic diseases from a focus on adult exposures to include prenatal events and exposures. This opens up the exciting possibility of preventing or mitigating many adult diseases and conditions.

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