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Review Article

Role of Epigenetics in Cardiac Programming During Pregnancy

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Abstract

Cardiovascular diseases have traditionally been viewed as a condition of aging individuals, and increasing focus has turned to its developmental origins. Birthweight has been related to cardiovascular disease risk. According to fetal origins of adult disease (FOAD) hypothesis, risk factors from intrauterine environmental exposures affect the fetal development and increase the risk of chronic diseases in adult life.

Keywords: Cardiovascular Diseases; Barker's Hypothesis; Birth Weight

Epigenetics/cardiac development

Development origins of adult disease

According to Barker's hypothesis, poor maternal nutrition during early fetal life increases the susceptibility of newborn to risk of cardiovascular disease in adult life. Also, low birth weight and fetal undernutrition is initiating factor in the development of cardiovascular disease according to DOHaD theory (development origins of adult disease). Fetal malnutrition can occur due to placental inadequacies and dysfunction has also have also been implicated in adult cardiovascular disease in offspring. According to fetal origins of adult disease (FOAD) hypothesis risk factors from intrauterine environmental exposures affect the fetus' development during pregnancy and increases the risk of chronic diseases in adult life [1-3].

Epigenetics/cardiac programming

Gene expression can be altered by epigenetics and these activities occur throughout the lifetime of an individual and affect the function of the corresponding products of gene expression products along with involvement of organs. Genetic modifications occur in response to environmental changes and accordingly switch on and off the genes via epigenetic modifications. Epigenetic changes can be done by lifestyle modifications, dietary modifications or possibly by using treatments strategies postnatally [1]. These epigenetic mechanisms are of great help in understanding the pathophysiology of various cardiovascular diseases and for finding potential diagnostic and therapeutic targets for treating these cardiovascular diseases. Epigenetic regulation occurs by DNA methylation, histone modification, or non-coding RNAs (ncRNAs) as small microRNA and long non-coding RNA are various epigenetic modifications that carry out regulation of genes and out of these DNA methylation and histone acetylation are the most important epigenetic mechanisms.

Epigenetic programming in adult patients with various cardiovascular diseases has been reported in many clinical studies [2]. Reports indicate that in addition to these, posttranscriptional regulations carry out their regulatory functions via non-coding RNA that in terms of cardiovascular disease susceptibility in adult cardiac patients [4-6].

Various post-natal events like lifestyle, age, and other disease conditions can cause CVD and the postnatal gene-environment interactions have been documented to promote CVD. Recently, there is development of understanding regarding *in utero* environmental changes causing prenatal development epigenetic programming of the fetus for development of roots of future CVD starting *in utero*. Changes occurring in fetal cardiac genes in IUGR state have been investigated by many researchers and one principle underlying molecular mechanism is epigenetic regulation which causes differential gene expression in IUGR fetuses when compared with normal fetuses. DNA methylation in IUGR have been reported to cause cardiovascular disease. Further studies to understand the mechanism of CVD and *in utero* gene-environment interactions are required.

Placenta performs various functions to support the growth of the fetus, prevention of fetal rejection by maternal immune system; and carry out transport/exchange of gases, nutrients, and waste products between mother and fetus. Also, it is involved in the fetal metabolism and produces many hormones to maintain pregnancy. During normal pregnancy there is a correlation between placental weight and birth weight. The development of placenta is affected in the state of altered maternal- fetal circulation.

Various determining factors especially diabetes result in placental dysfunction depending on the extent of exposure to hyperglycemia during fetal and placental development. Growth of placenta and fetus are severely affected and long-term uncontrolled hyperglycemia can also lead to placental vascular dysfunction in these women. In case of uncontrolled maternal hyperglycaemia, various histological changes such as immature villous, increased number of fetal capillaries, and fibrinoid necrosis of the placental villi occur in the placental tissues. Prolonged maternal insults occurring due to hyperglycemia, dyslipidemia, and hyperinsulinemia comprise the placental capacity to adapt and respond. This placental dysfunction can result in adverse fetal outcomes like IUGR.

Women with diabetes, reduced uteroplacental perfusion, and maternal vasculopathy can have intrauterine growth restriction and reduction in fetal growth. This abnormal placental vascular development decreases the normal placental blood supply causing hypoxia and reduced nutrient supply to fetus, resulting in IUGR fetus. There is redistribution of cardiac output in the fetus for increasing the fetal supply of oxygen and nutrient especially the supply to brain for its proper development. IUGR offspring have long term behavioural problems, neuropsychological malfunctions along with high rate of coronary heart disease, myocardial dysfunction, type 2 diabetes, hypertension, and stroke as adults and the underlying molecular mechanisms leading to fetal susceptibility to adult disease are still not clear. ironically, the clinical symptoms of cardiovascular disease in these IUGR babies usually strangely might not appear till adult life.

Barker's hypothesis

According to David Barker's hypotheses individuals with low birth weight, have a direct association with CVD in adulthood [3]. Epidemiological study of adults born at the time of Dutch famine (between 1944 and 1945) had a significant association between maternal starvation and low infant birth weight along with a high incidence of hypertension and coronary heart disease in them [7]. A high incidence of early onset coronary heart disease was reported among the persons conceived during the Dutch famine [7]. Barker hypothesized concept of fetal adaptation to prenatal environmental changes and their vulnerability to chronic diseases in adult life, and termed it as "fetal programming" and the concept was termed as "Developmental origins of health and disease (DOHaD)". In DOHaD, structural and functional changes occurring in fetal organs are due to extension of in utero maternal insults during postnatal life and these babies have increased susceptibility of chronic disease in adulthood. Fetal programming of other organs namely, brain, lungs, and hypothalamic-pituitary-adrenal (HPA) axis have been extensively studied. Still despite the fact that the programming of the heart is also very important, only few studies have investigated fetal programming of the heart and more research is required on this aspect [8].

Fetal programming of heart in IUGR

Heart being the first organ to develop and function during embryogenesis. The fetal organs developing during early embryogenesis are more vulnerable to the changes in the *in utero* environment as compared development of organs at the later stage of embryogenesis. Also, there is direct correlation between the amount of oxygen and nutrient supply to the fetus and if placental vascular dysfunction occurs owing to chronic hyperglycemia, there is reduced nutrient and oxygen supply to the fetus with resultant IUGR.

IUGR neonates have been reported to have significant changes in their cardiac morphology and subclinical myocardial dysfunctions are present at birth in these babies. Thus placental dysfunc-

tion occurring due to maternal diabetes along with undernutrition and hypoxia during cardiac remodelling leads to structural and functional changes in the developing myocardium. Thus, genomic changes due to *in utero* gene environment interaction results in cardiac remodelling due to impending IUGR.

Figure 1

Further research involving epigenetic mechanisms of cardiovascular programming in growth restricted fetuses is required.

Epigenetics of modifications and IUGR

The impact of intrauterine environment is currently under investigation for the future risk of cardiovascular and metabolic diseases and prenatal conditions can modify gene expression through epigenetic mechanisms to play an important role in the process of fetal programming. Before birth, due to an adaptive change of the fetus to adverse environment (lack of oxygen and nutrient supply) after delivery, altered metabolic responses occur in postnatal environment.

Epigenetic mechanisms, such as DNA methylation and histone modification, alter gene expression without involving a change in the nucleotide sequence and are therefore, important not only to the subject but also to future descendants and can be of help in reducing burden of cardiac remodelling in response to hypoxia, undernutrition occurring due to IUGR. IUGR has been documented to cause DNA methylation in a tissue-specific manner and further studies for understanding the epigenetic mechanisms in various tissues with direct impact on cardiac system would be beneficial [8]. There is dire need of uncovering the specific pathways of prenatal methylation of gene expression are required. These pathways are vital for the development and functioning of heart tissues. Only then the researchers would be able to link these pathways with the causation of specific cardiac diseases. DNA methylation occurring in the CpG islands have been documented in the clinical studies in samples obtained from affected IUGR offspring [8], however, they could not validate the causal link between these epigenetic modifications and various heart diseases. Also, studies have indicated that inheritable altered fetal cardiac genome is transferable from one generation to another and this phenomenon is termed as transgenerational programming of cardiac system [8,9].

Different genes have been studied to evaluate long-term epigenetic reprogramming [10], and Srebf2, gene which regulates cholesterol metabolism is altered in adults with diabetes mellitus and metabolic syndrome [11]. This gene has been demonstrated to produce effect on fetus via maternal lipid and glucose dysmetabolism during pregnancy. Srebf2 seems to be a potential candidate to mediate intrauterine environment-driven epigenetic changes and diabetic offspring health.

Epigenetic biomarkers can be of help for early prediction of risk of adverse events in cardiac high-risk individuals. Thus, use of epigenetic therapies in treatment of CVD will be good to include the atrial and ventral defects abnormalies in utero and also tetralogy of Fallot seems promising. Also, therapeutic agents such as inhibitors of DNA methyl transferase (DNMT), hormonal therapy, and certain dietary compounds have been documented to be beneficial in the treatment of cardiovascular diseases. In this context, many epigenetic- related therapeutic agents have been tested in pre-clinical trials for their possible use, but they are still awaiting approval to begin clinical trials and/or FDA approval.

Epigenetic mechanisms occurring during pregnancy and altered gene expression not only explain important aspects of the prenatal origin of cardiovascular and metabolic disease risk in adulthood, but also add significant complexity to pregnancy disorders, such as intrauterine fetal restriction and macrosomia that occurs during diabetes mellitus and hypertension. Future research would assess the important facet of epigenetic modifications affecting neuronal cholesterol metabolism.

Conclusion

Epigenetic mechanisms occur during pregnancy and altered gene expression occur during this period. This aspect explains the important aspects of prenatal origin of cardiovascular and metabolic disease risk in adulthood, along with complexities to pregnancy disorders such as intrauterine fetal restriction and macrosomia that occur during diabetes mellitus and hypertension. Future research would assess the important facet of epigenetic modifications affecting fetal growth paving way for epigenetic markers and therapeutic modalities.

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