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The role of fetal programming in human carcinogenesis – May the Barker hypothesis explain interindividual variability in susceptibility to cancer insurgence and progression?

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Abstract. – The growing incidence of cancers is pushing oncologists to find out new explanations other than the somatic mutation theory, based on the accumulation of DNA mutations. In particular, the embryo-fetal exposure to an increasing number of environmental factors during gestation might represent a trigger able to influence the susceptibility of the newborn to develop cancer later in life. This idea agrees with the fetal programming theory, also known as the Barker hypothesis. Here the role of insulin-like growth factors, thymosin beta-4, and epigenome are discussed as mediators of cancer in prenatal human development. The role of epigenetic factors that during gestation increase the predisposition to develop cancer and the similarities in the gene expression (like MMP9, OPN, TP53 and CDKN2A) between embryonic development and cancer are key factors. Likewise, maternal obesity might be able to re-program embryo-fetal development with long-term changes, including an increased risk to develop neuroblastoma and acute leukemia. Birth weight alone and birth weight corrected for gestational age are proposed as important variables capable of predicting the vulnerability to develop cancers. According to the findings here reported, we hypothesize that cancer prevention should start during gestation by improving the quality of maternal diet. In conclusion, the Barker hypothesis should be applied to cancer as well. Therefore, the identification of the epigenetic factors of cancer appears mandatory, so that the cancer prevention might start in the womb before birth.

Key Words:
Fetal programming, Barker hypothesis, Cancer, Birth weight, Fetal epigenome, Maternal diet during gestation.

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Introduction

The growing incidence of cancers across all age categories around the world, particularly in Western countries, is pushing oncologists and researchers on their origin[1]. The dominant pathogenetic model of carcinogenesis, known as the somatic mutation theory (SMT), based on the accumulation of DNA mutations, does not fully explain the increase in cancer incidence in children and young adults[2]. More recent hypotheses suggest that the embryo-fetal exposure to an increasing number of environmental triggers (first hit) might act as a disease primer, making newborns more susceptible to subsequent environmental exposures later in life (second hit). This eventually triggers the carcinogenic pathways[3].

Lifestyle-related factors, environmental agents, obesity, accumulation of many new carcinogenic factors in the environment, and food contamination by additives have been indicated as possible causes for explaining the increasing incidence of cancer[4]. Thus, the fetus is highly vulnerable to multiple exogenous factors. Fetal exposure to carcinogenic environmental agents during the intrauterine life, a critical time window for development, might cause significant architectural and cellular changes in organs and tissues that persist later in life[5,6]. According to the Barker hypothesis, also known as the fetal programming theory, the exposure to multiple environmental factors in utero can have profound impact later in life, determining the predisposition, or alternatively the resistance, to multiple diseases[7-9].

The Role of Insulin-Like Growth Factors (IGFs)

Recent published studies, evidenced a possible role for fetal programming in determining the risk of the development of some cancers in childhood, including acute lymphoblastic leukemia[10]. In that study, the linkage between the changes in fetal growth and the susceptibility to develop some cancers later in life has been identified in the biological mechanisms involving the Insulin-like growth factors (IGFs). The IGF system has been considered at the crossroad between fetal development and cancer, being implicated both in the development during the intrauterine life as well as in the insurgence of some specific cancers, including colon, breast, prostate and lung cancer[11]. This could be explained with the role of IGF that is a natural growth hormone and plays crucial role in normal growth and development. It is widely demonstrated that IGFs are essential for growth and survival, suppressing apoptosis and promoting cell cycle progression, angiogenesis, and metastatic activities in various cancers. New research lines are considering IGF targeted therapies for cancer. Strong preclinical evidence and ongoing clinical trials have resulted in the approval of several new agents for cancer treatment[12].

The Role of Thymosin Beta-4 in Both Development and Cancer

A similar role, at the crossroad between fetal development and cancer, has been suggested for thymosin beta-4 (TB-4), a small peptide highly expressed during the intrauterine life[13]. TB-4 is down-regulated in the postnatal life, as demonstrated by the lower levels of this peptide in the saliva of adult subjects compared to the high levels in the saliva of pre-term newborns[14]. This peptide is also highly expressed in colorectal cancer, particularly in tumor cells at the invasion front of the tumor[15]. The association between the role of TB-4 in physiology and in cancer was underlined by the process of epithelial-mesenchymal transition (EMT), a fundamental mechanism during embryogenesis and development[16] as well as in invasion and cancer metastasis[17]. The involvement of IGF and TB-4 both in fetal growth and in cancer development reinforces the hypothesis that some molecular programs, utilized in physiological conditions during fetal development, might be silenced in the postnatal life, and re-utilized by cancer stem cells during carcinogenesis[18].

Fetal Growth and Childhood Cancer: the Nordic Population Study

According to the Barker hypothesis on the relationship between derangement during the fetal growth and susceptibility to develop multiple diseases later in life[19], a case control study[20] was carried out in 17,698 Denmark, Norway, Finland and Sweden children born from 1967 to 2010. In this study, the risk of acute myeloid leukemia was increased in children born small for gestational age. In contrast, the risk for Wilms tumor was higher in children with a birth weight >4,000 g. Moreover, newborns large for gestational age had a higher risk for developing soft tissue tumors in childhood. Eventually, the authors concluded that changes in fetal growth are associated with several childhood tumors, supporting the hypothesis that carcinogenesis might start in utero even for tumors clinically presenting later in life. For the

analysis of potential association in subsequent age class, results will be released in the future with the subsequent rounds of follow-up.

The Epigenome in Prenatal Development as a Mediator of Cancer

Further data on the possible fetal origin of neoplasms presenting in childhood and adulthood were reported in a study on the epigenetic events that establish gene expression signature during development[21]. According to this study, environmental factors, acting on fetal tissues during gestation might disrupt the epigenetic programs, dysregulate the fetal epigenome potentially impacting the susceptibility of the newborn to diseases, including cancer later in life. Among the multiple epigenetic factors that play a major role on the fetal epigenome, maternal diet during gestation and during breast feeding was identified as the most important potential mediator of epigenetic changes regarding the predisposition to develop cancer in childhood and adulthood[21,22]. On this basis, the authors suggested that cancer prevention should start during gestation with an optimal modulation of prenatal development. According to Kaur et al[21], efforts should be encouraged to identify maternal dietary interventions during gestation and lactation that can be beneficial in preventing cancer development later in life.

Fetal Epigenome and Cancer: Experimental Evidence

An important contribution to the identification of the epigenetic factors acting during gestation that might increase the susceptibility to carcinogenesis later in life comes from studies carried out in experimental animals[23]. Maternal alcohol assumption during gestation, resulting in fetal alcohol exposure during gestation, and during the perinatal period has been shown to increase the vulnerability of the offspring to insurgence and progression of cancer. The linkage between maternal alcohol assumption and the increased susceptibility to cancer insurgence might be represented by the ability of alcohol to interfere with the development of the immune system, leading to immune incompetence of the offspring and a decrease of tumor surveillance. Moreover, excessive maternal estrogen assumption during gestation, resulting in estrogenization during prostate development, was demonstrated to promote tumor progression in the prostate gland, ending with the insurgence of prostate adenocarcinoma[24].

Similarities in Gene Expression Between Embryogenesis and Cancer

Interesting data on the similarities in multiple gene expression patterns, between embryogenesis and cancer, have been published in a study[25] carried out on fetal liver and primary and metastatic liver tumors. In this study, the expression of fourteen candidate genes was analyzed by real-time quantitative reverse transcription PCR. Four genes, Matrix metalloproteinase 9 (MMP9), Osteopontin (OPN), Tumor protein 53 (TP53) and Cyclin-dependent kinase inhibitor 2A (CDKN2A) were found to be expressed in a similar pattern during early embryonic development, in primary liver tumors and in metastases. These findings clearly indicate that these four genes are activated during fetal development and that they are re-expressed in primary liver tumors and in cancer metastasis. These similarities at gene expression level between fetal and cancer cells reinforce the hypothesis that changes in fetal development, due to impaired fetal growth, might predispose the neonate to a re-expression of these "fetal" genes and related molecular pathways in childhood or in adulthood. That predisposes the newborn with intra-uterine growth restriction (IUGR) to the insurgence of cancer later in life.

Fetal Reprogramming Due to Maternal Obesity

Intriguing data on fetal programming of adult diseases have been reported in a study on the effects of maternal obesity on long-term outcomes for the offspring[26]. During obese pregnancy, fetuses should re-program organs and tissues development, due to the altered metabolic landscape, leading to log-term changes in structure and function[27]. Fetal re-programming related to maternal obesity has been defined as the developmental over-nutrition hypothesis[28]. Maternal obesity during gestation has been associated with an increased birth weight and with an increased risk, for the newborn, to develop neuroblastoma[29] and acute leukemia[30]. Moreover, a high birth weight represents a risk factor for the development of prostate cancer[31,32] and testicular cancer[33,34] later in life. The association of maternal early-pregnancy dietary glycemic index with childhood general, visceral, and abdominal fat accumulation has been confirmed in a recent cohort study[35] among 2,488 Dutch pregnant women and their children.

Birth Weight and Susceptibility to Develop Cancer Later in Life

From a practical point of view, in clinical practice, the knowledge of the birth weight corrected for gestational age and of the birth weight alone might be utilized as a risk factor for development of leukemia and central nervous system tumors in childhood[36-39]. Fetal macrosomia should be considered a risk factor for the insurgence of multiple diseases, including cancer, in childhood as well as in adulthood[40]. At experimental level, feeding pregnant rats with a high-fat diet supplemented with ethinyl-oestradiol increased significantly mammary cancer risk in daughters, granddaughters, and great-granddaughters[41]. In this study, the effects of maternal high fat and oestrogen exposure during gestation on offspring's breast cancer incidence were associated with changes in DNA methylation in the mammary glands of all three generations. These findings may suggest that dietary and oestrogenic exposure during gestation may increase mammary cancer risk for multiple generations, through epigenetic mechanisms.

Maternal Polyinsaturated Fatty Diet as a Fetal Programming Factor

In a recent study[42], transgenerational increase in breast cancer risk has been observed in pregnant mice following intake of high n-6 polyunsaturated fatty acid diet during gestation. In this study, 1,587 and 4,423 differentially expressed genes between control offspring and offspring from dams on high fat diet were identified in F1 and F3 generations, respectively. Moreover, the Notch signaling pathway was found to be upregulated in high fat offspring. Finally, ten node genes in high fat diet offspring were connected to genes linked to increased cancer risk, increased resistance to chemotherapy and poor prognosis. In female neonates, multiple intrauterine events have been associated with an increased risk for developing breast cancer in adulthood[43-45].

Should Cancer Prevention Start in the Womb?

These data taken together induced some authors to suggest the necessity, in the era of obesity pandemic that we are facing in these years, to also focus on the maternal womb, and the intrauterine life, as the target for starting cancer prevention[46]. Should we consider this the "true" primary prevention? The hypothesis that prevention should start in the perinatal period had been previously proposed for renal insufficiency presenting in adulthood[47,48]. A better understanding of the effects of maternal obesity for offspring, particularly regarding the possible increased risk for developing multiple cancers in adulthood, is crucial. Prevention of some neoplasms typical of the pediatric age, including acute lymphoblastic leukemia, might have roots in the prenatal phases. Neoplasms should be likely included among the human diseases whose incidence is programmed before birth[49].

Maternal Diet Quality and Fetal Programming of Cancer

Maternal diet quality has been demonstrated to represent a risk factor for childhood leukemia even in the year before pregnancy[50,51]. In these studies, the quality of maternal diet and the absence of vitamin supplements in the diet before pregnancy was associated with a major risk of insurgence of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). Taken together, these findings suggest that many dietary components in the maternal diet during gestation as well as in the year before pregnancy might influence childhood leukemia risk. On the contrary, high maternal consumption of vegetables and fruits has been associated with a reduced risk of ALL in childhood[52].

DNA Hypermethylation and Fetal Programming of Cancer

Famine exposure during gestation has been associated with intra-uterine growth restriction and with persistent epigenetic changes, including DNA hyper-methylation[53,54]. Moreover, the DNA methylation signature related to marked dietary deprivation during gestation, have been shown to be sex-specific and related to the timing in the prenatal period[55].

Discussion

According to the David J Barker's fetal origins hypothesis, the nine months of intrauterine life represent one of the most critical phases in a human being's life, where future abilities and health trajectories are shaped, and susceptibility or resistance to multiple diseases is programmed[56]. The fetal origins hypothesis combines several key ideas[57]: i) the effects on health of fetal growth persist throughout the entire life; ii) the health effects of fetal programming may be

latent for many years after birth; iii) fetal programming reflects the effects of the environment on the fetal epigenome.

The Barker hypothesis has been applied to multiple diseases, including ischemic heart injury[7,19], impaired glucose tolerance[58], insulin resistance[59], elevated serum cholesterol concentrations[60], hypertension[61], stroke[31,62,63], and metabolic disease[64]. Moreover, fetal programming has been implicated in the insurgence of neuropsychiatric disorders[65-68], and in the susceptibility to undergo severe kidney disease and renal failure later in life[69,70]. In more recent years, the role of fetal programming has been analyzed in genetic diseases, including Wilson's disease[71] and in the susceptibility to develop severe lung injury following COVID-19 infection[70]. Based on these studies, the hypothesis is that regenerative medicine should start in the prenatal period, favoring the exposition of the embryo and the fetus to epigenetic factors, including nutrients, indispensable for an optimal fetal development, and avoiding all the epigenetic factors able to modify human development[47,48,72-74]. In this review, the available data supporting the hypothesis that fetal and perinatal programming might shape our susceptibility to develop at least some cancers in childhood and in adulthood are reported. One of the most intriguing findings emerging from this study, is the involvement of multiple genes and molecular pathways both during the physiological fetal development and in cancer insurgence and progression.

Conclusions

Data here reported suggest that cancer cells may re-capitulate some molecular programs utilized in the intrauterine life. According to this view, we hypothesize that changes in normal development due to epigenetic factors acting during gestation could permanently change some molecular pathways involved in cell proliferation, leading to susceptibility to develop some cancers later in life. The identification of these epigenetic factors is mandatory, so that cancer prevention might start during gestation, with an optimal modulation of prenatal development. To this end, efforts should be encouraged to identify maternal dietary interventions in the prenatal period that can prevent cancer development in children and adults. We hope that this new way of thinking will allow a science-based view to the next phase of our response to cancer as well as that the new approach, based on the Barker's hypothesis, might reframe our policy towards cancer prevention in the near future.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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