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Can Loss of Imprinting in the Placenta Serve as a Biosensor of the Perinatal Environment?

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It is well known that environmental exposures are risk factors for most common complex diseases and that environmentally induced phenotypes are associated with epigenetic changes to the genome. For example, factors such as diet, hormones, toxins, and stress can result in cellular DNA methylation and chromatin modification changes that affect gene expression and disease susceptibility [1]. There is also increasing evidence that early life nutrition is involved in fetal programming for the development of multiple diseases later in life, including heart disease, diabetes, obesity, and cancer [2]. The placenta serves as the maternal-fetal interface during pregnancy for the exchange of nutrients, gases, and waste between the blood supplies of the mother and child. Inadequate placentation results in poor fetal nutrition and is a leading cause of intrauterine growth restriction (IUGR) worldwide. Thus, by directly regulating fetal nutrient supply, the placenta plays a central role in fetal programming and is thought to carry valuable information about the perinatal environment experienced by the offspring [3].

Genomic imprinting is an important epigenetic mechanism of gene regulation that is set in the developing egg and sperm cells resulting in parent-of-origin specific monoallelic expression. Genomic imprints are essential for both normal fetal and placental development. Interestingly, imprinting arose with the evolution of placental mammals and the great majority of imprinted genes that have been identified are expressed in the placenta [4]. Imprinted genes affect placental function in two major ways: (i) by affecting the structural development of the placenta, and (ii) by affecting nutrient transfer systems [5,6]. Imprints are generally fixed in somatic cells throughout embryonic development and adult life; however, several groups have reported biallelic expression of imprinted genes in first trimester placenta that appears to resolve to the expected monoallelic imprinted expression at term [7-9]. These findings suggest that imprinting may become established or modified in a cell lineage or developmental stage-specific manner in the human placenta. In addition, imprinted genes are dosage sensitive and alterations in expression levels can have deleterious effects on fetal development and postnatal metabolism. Indeed, several studies have shown an association of either loss of imprinting (LOI) or altered imprinted gene expression levels with preterm birth, preeclampsia, and IUGR [9-13]. Thus, epigenetic regulation of imprinted genes might render them susceptible to environmental perturbation, making them potential biosensors of the perinatal environment and possible biomarkers for predicting risk of fetal and future adult disease [14].

Imprinted genes are frequently found in clusters in the genome and their allele-specific expression is regulated by an imprinting control region (ICR). ICRs function to repress genes on the same allele, while methylation inactivates ICRs, allowing expression of genes in *cis*. The ICR obtains a new parent-specific CpG methylation imprint during gametogenesis; hence, they are called germline differentially methylated regions (DMRs). Some imprinted gene clusters also contain secondary DMRs, which are generally located in gene promoter regions. The methylation marks of these DMRs are erased and reprogrammed in the zygote after fertilization and are dependent on the presence of an ICR. The developmental stage at which these somatic DMRs acquire differential methylation varies and can be tissue-specific. In addition, secondary DMRs often acquire methylation after imprinted expression of the gene associated with it has already been established [15].

The placental epigenome is unique, in that it is hypomethylated relative to embryonic and adult tissues [16]. In addition, the methylcytosine content is gestational age dependent and increases by ~10% between the first and second trimesters; yet, the term placenta reaches at most 80% of that observed in fetal tissues or adult blood [17]. Similarly, the epigenetic mechanisms involved in establishing and maintaining genomic imprints are distinct in the placenta, where repressive histone modifications have been reported to maintain silencing of the imprinted allele independently of DNA methylation [18,19]. Although environmentally induced phenotypes are associated with epigenetic changes in DNA methylation patterns, histone modifications, and chromatin structure, it is not clear how environmental exposures modify the effects of imprinted genes. Even so, the susceptibility of imprinted genes to environmental alteration is likely locus or gene specific, depending on the developmental time point and the imprinting mechanism employed. Moreover, LOI that occurs during epigenetic reprogramming in early development is expected to affect a large proportion of cells and would likely be reflected in both the fetus and placenta.

Contrary to the idea that imprinted genes might be susceptible to environmental perturbations is that the converse might be true: imprinted genes might be protected from alteration because of their epigenetic modifications [20]. Clearly, ICR's retain their imprinted marks during the global demethylation events that occur in the zygote following fertilization. On the other hand, secondary DMRs are erased at that time and are remethylated in a parent-of-origin dependent manner at varying time points in development. While we know very little about the function of secondary DMRs in the regulation of imprinted gene expression or the *cis*-acting mechanisms and trans-acting factors that establish DNA methylation at these DMRs, it appears that imprinted gene expression is not strictly correlated with the methylation status of these DMRs [15]. Thus, there are many questions regarding the mechanisms involved in establishing, maintaining, and erasing

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genomic imprints; however, the data available on LOI are insufficient to draw a firm conclusion at this time as to whether imprinted genes are more or less vulnerable to environmental changes.

A recent study on the effects of environmental endocrine disruptors on epigenetic perturbation of imprinted genes provides some insight into this question. Pregnant mice were exposed to bisphenol A (BPA), phthalate (DEHP), or vinclozolin at mid-gestation for 5 days and allele-specific expression of a large number of imprinted genes was analyzed in embryonic and extra-embryonic tissues. The investigators observed little LOI in the placenta or embryonic tissues for the majority of imprinted genes, with the exception of *Slc22a18* and *Rtl1as* in the embryo and/or the placenta after treatment with BPA. There was also an endocrine disruptor specific increase in variability of allele-specific expression for several other imprinted genes [21]. The authors concluded that monoallelic expression of imprinted genes might be relatively insensitive to disruption by these chemicals, although they are not completely immune to the effects. However, this pilot study only tested a single dose of each endocrine disruptor in a limited time-frame during pregnancy, and it is unknown whether these chemicals might have a more pronounced affect on imprinting in earlier developmental stages, or on the developing germ cells, which would lead to a transgenerational effect. Nevertheless, this study provides additional evidence that imprinted genes may exhibit locus-specific regulatory mechanisms. Thus, further investigation of the effects of perturbations of the perinatal environment on imprinted gene expression should be studied for each individual locus.

In addition, there is increasing evidence that *in vitro* fertilization and embryo culture can alter imprinted gene expression in the placenta as well as the embryo [22]. In humans, IUGR and several congenital imprinting disorders, such as Beckwith-Weidemann and Silver-Russell syndromes, occur at significantly higher frequencies in children conceived with the use of assisted reproductive technologies (ART) than in children conceived spontaneously. Whether ART introduces imprinting errors or whether epimutations are more frequent in individuals with infertility remains an open question [23]. Nevertheless, there is an increased appreciation that intrauterine and environmental factors might modify the placental epigenome, including imprinted genes, which in turn, could potentially adversely affect fetal growth and development.

The advantages of using placental tissue for the identification of biomarkers of exposure and risk of disease are many. First, placental tissue can be sampled during pregnancy and is readily available after birth of the infant. Second, the large tissue size provides ample material for multiple testing. Third, the placenta is an important site of imprinted gene action and many more imprinted genes are expressed in placenta than in peripheral blood. Fourth, the relative abundance of different cell types in placenta is not known to be altered by environmental stress, as it is in blood. Finally, because the placenta serves as the gateway to developing offspring, it records exposures that occurred during a limited, but critical developmental time frame, and alterations to the epigenetic signature are not further complicated by exposures later in life.

Additional studies into the effects of the perinatal environment on genomic imprinting are necessary to determine whether LOI will be a useful measure of in utero exposures and prediction of risk for subsequent disease development. LOI measurements are appealing because they focus on a limited number of loci as opposed to assays that measure the effects of alterations in global DNA methylation. Combinations of imprinted loci that are determined to be susceptible to perturbations could be further explored in cohort studies of exposed individuals. If such a LOI signature were validated in large-scale human studies, they could then be used to monitor the perinatal environment for adverse conditions, with the goal of identifying optimal strategies for improving maternal health during pregnancy, which would have a significant positive impact on pregnancy out comes and on both the immediate and long-term health of women and children.

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