Unravelling the Link Between the Placental Epigenome and Pregnancy Outcomes

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Placental dysfunction underlies common and serious pregnancy complications such as fetal growth restriction (FGR), pre-eclampsia, preterm birth, and pregnancy loss. Although these complications most frequently manifest in mid- to late gestation, the origins of placental dysfunction often arise in early pregnancy and include maternal factors such as vascular insufficiency, smoking, and metabolic challenge [1]. Unfortunately, the mechanisms behind these conditions remain poorly understood. There is, however, increasing evidence that placental dysfunction from a variety of causes is associated with an altered epigenetic profile in the late-gestation placenta [2–5].

Recent work is beginning to uncover how the placental epigenome responds to the pregnancy environment. The epigenome contains three classes of tractable, quantifiable, and accessible information about the exposures of pregnancy. First, placental DNA contains programmed epigenetic foundations that are distinct from those of the fetus and essential for normal placental function, such as the hypomethylation of retrotransposon-derived genes [6–12]. Second, DNA methylation in the early embryo can be altered in response to environmental factors, leading to lifelong phenotypic change, as shown in mouse paradigms [13]. Third, the fetal epigenome can respond to different environments of pregnancy (obesity, insulin sensitivity, hypoxia, etc.) such as through changes in placental transporter genes [1]. The responsive nature of the placental epigenome may benefit fetal growth in suboptimal pregnancy conditions; however, it also may contribute to the development of pregnancy-related pathologies, such as FGR.

The importance of epigenetics in the placenta has been highlighted by findings that show that epigenetic aberrations interfere with normal placental and fetal growth [14, 15]. However, it is unknown which specific epigenetic events compromise placental function, induce pregnancy-related pathologies, and have long-term effects on the fetus. Care, therefore, must be taken when attributing causality for these outcomes to epigenetic changes in late gestation [16]. The manuscript by Leeuwerke et al. [17] in a recent issue of *Biology of Reproduction* adds important information to this question by analyzing placental methylation patterns of genes associated with FGR from first trimester chorionic villus biopsy samples in pregnancies that continued to term. In contrast to the DNA methylation changes that have been reported in several genes in term placentae of infants born with either intrauterine growth restriction or small for gestational age (SGA) (reviewed in [18]), Leeuwerke et al. did not find any methylation differences in the placental samples obtained at a median gestational age of 11.3 wk between those pregnancies that went on to deliver an SGA baby at term and those that delivered an appropriately grown baby. These data indicate that the methylation changes associated with FGR must arise in the second or third trimesters. Also of note is that one-third of the mothers of SGA pregnancies were smokers whereas none of the control pregnancies were. Smoking in pregnancy is a major cause of FGR and has been associated with changes in the methylation profile of placental DNA at term [5]. If smoking-related epigenetic changes arose in early pregnancy, one might have expected to see differences in methylation profiles between SGA and control cases. Overall, the data reported by Leeuwerke et al. support the hypothesis that the methylation changes previously reported in term placentae are a consequence of the pathological pregnancy and may not be causally related to the pathology or, indeed, even the consequences, such as growth restriction.

This last point requires further research. Although most FGR becomes apparent in the third trimester, with more severe cases presenting in the second trimester, there is circumstantial evidence suggesting that size at birth may be determined, at least in part, in the first trimester [19, 20]. It clearly is not possible to obtain placental samples beyond the first trimester, except at delivery, but newer techniques such as profiling of fetal and placental DNA in maternal plasma [21] may facilitate further insights into the timing of the changes in the epigenetic profile in pregnancies complicated by placental dysfunction and a greater understanding of cause and consequence.

Searching for a methylation change in the epigenome can be like looking for a needle in a haystack. Although Leeuwerke et al. analyzed candidate genes for FGR that were supported by the literature, their study may have benefited more from performing a genomewide analysis to detect methylation changes associated with FGR in first trimester placenta. The rapidly advancing field of genomics has greatly improved the tools available for genomewide epigenetic analysis. The cost of genomewide studies has drastically reduced in recent years, making it a relatively small investment for an incredible amount of data. Genomewide methylation data, generated from either reduced representation bisulfite sequencing [22] or whole genome bisulfite sequencing [23, 24], would be a tremendous resource to investigate placental dysfunction in FGR pregnancies. Mining of such data could reveal how the placental epigenome responds to environmental stimuli, which