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Characterizing the lipid and metabolite changes associated with placental function and pregnancy complications using ion mobility spectrometry-mass spectrometry and mass spectrometry imaging

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ABSTRACT

Successful pregnancy is dependent upon discrete biological events, which include embryo implantation, decidualization, and placentation. Problems associated with each of these events can cause infertility or conditions such as preeclampsia. A greater understanding of the molecular changes associated with these complex processes is necessary to aid in identifying treatments for each condition. Previous nuclear magnetic resonance spectroscopy and mass spectrometry studies have been used to identify metabolites and lipids associated with pregnancy-related complications. However, due to limitations associated with conventional implementations of both techniques, novel technology developments are needed to more fully understand the initiation and development of pregnancy related problems at the molecular level. In this perspective, we describe current analytical techniques for metabolomic and lipidomic characterization of pregnancy complications and discuss the potential for new technologies such as ion mobility spectrometry-mass spectrometry and mass spectrometry imaging to contribute to a better understanding of the molecular changes that affect the placenta and pregnancy outcomes.

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1. Introduction

A prerequisite for successful mammalian reproduction is effective, two-way interactions between an implantation-competent blastocyst and the receptive uterus, especially since the blastocyst will only implant when molecular dialogue between these entities is established. In women, the uterus becomes receptive for only a short period, typically 7–9 days after ovulation (cycle days 21–23) during the mid-luteal phase, and after this period it becomes refractory (nonreceptive) and remains this way for the rest of the luteal phase. Unfortunately, even after implantation there are many possible problems that can occur in the uterus. Deep placentation is one of the primary pregnancy transformations that can lead to problems such as preeclampsia (PE), intrauterine growth restriction, preterm labor, and placental abruption [1]. Deep placentation normally occurs due to invasion of the placental bed by the extravillous trophoblast, involving the decidua and the inner (junctional zone) myometrium. Because the placenta is a complex organ composed of heterogeneous cell types and substructures that undergo a variety of processes for normal development (Fig. 1), multi-omic studies are required to more fully understand the molecular changes that affect the placenta and associated pregnancy.

To better understand the molecular changes in the placenta, a previous study explored the distinct lipids found in the chorionic plate (composed primarily of fetal cells) and the basal plate (consisting of a mixture of fetal (trophoblast) and maternal cells), since different amounts of specific lipids in distinct placental regions have been indicated in pregnancy problems [2]. As expected, most lipids were common to both sides of the placenta and were present in comparable abundance. However, twelve lipids (with the majority being phosphatidylcholines (PC) and two sphingomyelins (SM)) differed significantly in their intensity between the chorionic plate and basal plate tissue with most having a higher abundance in the basal plate. This regional selectivity was thought to be from the implantation of the blastocyst in the uterine wall that is accompanied by a transformation of the endometrial lining into decidua. The decidua eventually becomes the maternal cells in the placenta,

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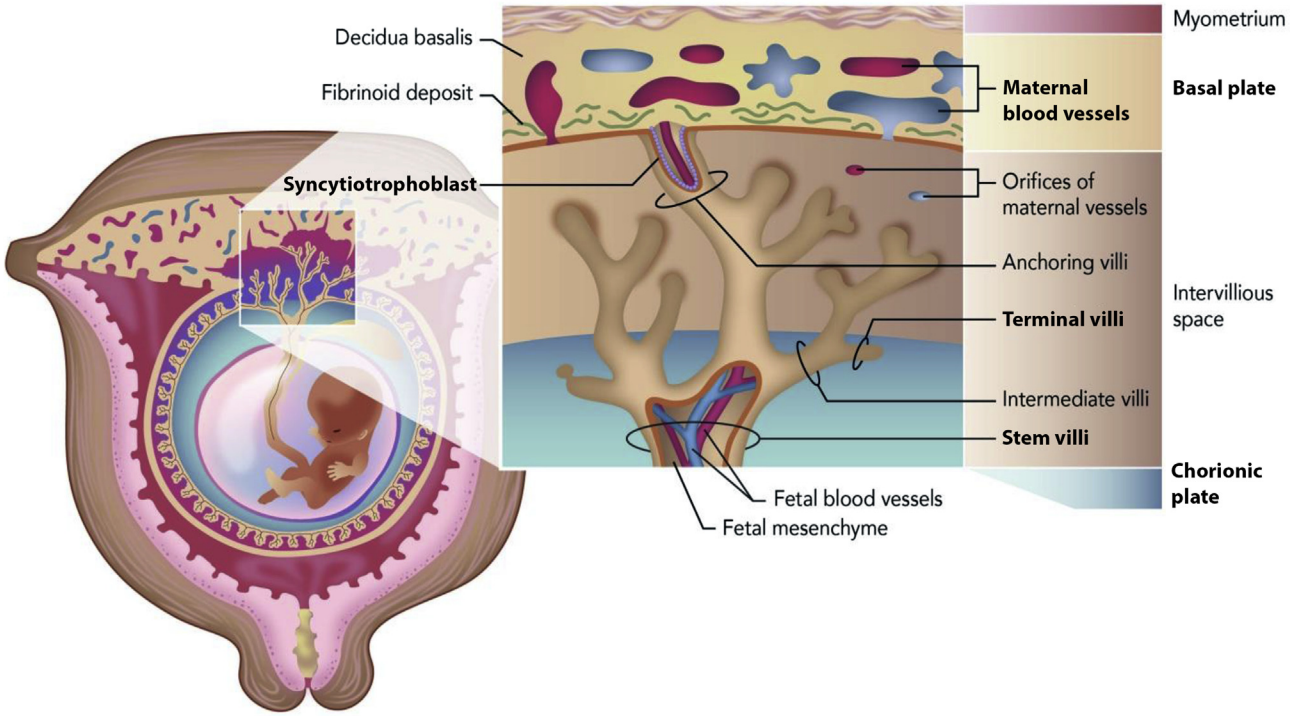

Fig. 1. The placental regions of importance in normal pregnancies and those associated with complications. The maternal blood vessels, basal plate, terminal villi, stem villi, chorionic plate, and syncytiotrophoblast regions are all bolded in this figure to illustrate their importance in pregnancy complications.

which are more common in the basal plate, resulting in higher concentrations of lipids in this area [2]. Biofluids have also been analyzed to characterize differences in the fetoplacental and maternal metabolites in pregnancies with poor outcomes compared to normal pregnancies. The goal of many of these studies was to gain insight into PE, a multi-system disorder of pregnancy that is the leading cause of maternal death [3,4]. PE is hypothesized to arise from circulating molecules derived from an unhealthy placenta, therefore many of these studies leverage metabolomics and lipidomics of plasma [5–8] and serum [9,10]. By comparing longitudinally acquired biofluid samples for both women who subsequently developed PE and those with normal pregnancies, researchers have been able to elucidate potential clues to both the etiology and pathogenesis of PE. Common findings between these studies have linked PE to dysregulation of carnitine species, amino acids, phospholipids (i.e., increased phosphatidylserine (PS) species) and sterol lipids [5,6,8,11], and other perturbed small molecules, including vitamin D metabolites and sphingolipids. Many of these molecules are also dysregulated in serum samples associated with placental abruption [12] with the pregnancies ending in poor outcomes (small gestational age infants, preterm birth, or neonatal intensive care admission) [13].

Researchers have also leveraged nuclear magnetic resonance spectroscopy and mass spectrometry-based multi-omic characterizations to identify which molecules exhibit differential expression or abundances in PE versus healthy human placental tissues [8,13,14]. Lipidomic analyses of placenta from patients with PE have shown similarities to plasma studies in that they also revealed PS as the most prevalent phospholipid species showing increased levels when compared with control placenta samples [8]. Collectively, these studies also show that lipid dysfunction could start as early as embryo implantation in pregnancies destined for PE development. Further, Dunn and colleagues reported significant changes in diglycerides, triglycerides, phospholipids, sphingolipids, fatty acids and fatty acid carnitines as the placenta develops between early and late first trimester pregnancies [13]. This same study also compared placental tissue from term-uncomplicated pregnancies with those exhibiting PE at term and found significant changes in mitochondrial metabolism (i.e. fatty acid beta-oxidation), vitamin D metabolism and oxidative stress. Oxidative stress can greatly alter the placenta metabolome [15], and some changes in placental phenotype seen in PE can be reproduced by exposing placental explant cultures to altered oxygen tension [16–18]. In this paper, we highlight analytical tools enabling researchers to create a blueprint of the lipidomic and metabolomic architecture for monitoring pregnancy and those molecular changes underlining pregnancy complications. Further, we discuss the potential of new techniques for improved future analyses.

2. Conventional metabolomics tools for understanding pregnancy complications

Analytical tools such as nuclear magnetic resonance spectroscopy (NMR) and mass spectrometry (MS) have previously captured changes in metabolites and lipids from maternal body fluids such as plasma and serum, placental tissues and explant cultures, and syncytiotrophoblast microvesicles (Fig. 1). NMR is inherently quantitative and offers the ability to elucidate molecular structures, but suffers from low measurement sensitivity and throughput [19,20]. On the other hand, MS analyses are highly sensitive and can be used alone or in conjunction with front end separations like liquid chromatography. One of the most powerful uses of MS alone to study pregnancy complications has been with mass spectrometry imaging (MSI). MSI technologies have previously been used to characterize the high and diverse lipid content of decidua [21–24]. MSI has also been applied to normal human placentas and used to determine the specific distribution of SM(d18:1/16:0) in the stem villi and PC(16:0/20:4) in the terminal villi [25]. Alterations in the

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