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Preliminary evidence of a paternal-maternal genetic conflict on the placenta: Link between imprinting disorder and multi-generational hypertensive disorders

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ABSTRACT

There has been great research progress on hypertensive disorders in pregnancy (HDP) in the last few decades. Failure of placentation, especially a lack of uterine spiral artery remodeling, is the main pathological finding of HDP. Currently, members of the vascular endothelial growth factor family are used as markers for the early prediction of onset of HDP. Epidemiologic research has also shown that HDP can have effects on the next generation infants, representing a Development Origins of Health and Disease-related disease. However, the precise pathogenic mechanism and the effect of HDP on the offspring remain unclear. The group of strong pro-inflammatory molecules known as "danger signals" have been shown to be released from the placental trophoblast surface and increase in the maternal circulation in HDP, which are then possibly transported into the fetal circulation. These signals, including fatty acids or adipocytokines, may alter the offspring's health in later life. Moreover, a hypoxic condition alters placental methylation, and the change may be passed onto the fetus. Although the genetic origin of the disease is still unknown, a hypothesis has been put forward that a paternal-maternal genetic conflict, mainly at imprinting lesion sites, may be a key factor for disease initiation. In particular, an imbalance in paternal and maternal factors may impede proper placentation, trophoblast invasion, decidualization or immune moderation so as to achieve better nutrition for the fetus (paternal) versus ensuring safe delivery and further pregnancy (maternal). Here, we review this research progress on HDP and focus on this novel genetic conflict concept, which is expected to provide new insight into the cause, pathophysiology, and multi-generational effects of HDP.

1. Introduction

Great insight and progress have been made into understanding the causes and nature of hypertensive disorders in pregnancy (HDP) in recent years. Although several hypotheses have been proposed in relation to the pathogenesis of HDP, the majority have remained unconfirmed; however, new findings in this century have begun to unveil the pathophysiology of HDP. Research in this field has focused on exploration of the roles of cytokines, physiology, pathology, genetic factors, and epidemiology, among other topics [1]. One of the main advances in this field came with recognition of the importance of a failure in placentation as a first stage of the disease, serving as the platform of the feto-maternal interface in every stage of pregnancy, which determined the "two-stage theory" of HDP [2]. In this review, we focus on recent progress made in research on HDP, including discovery of the role of "danger signals" or related adipocytokines and the concept of Developmental Origins of Health and Disease (DOHaD). In particular, we discuss the recently proposed paternal-maternal genetic conflict hypothesis to explain the placental effects in HDP, which shows great potential to provide new insight into the cause of the disease.

2. HDP: a central disease of emergency pregnancy complications

HDP involves hypertension that occurs after 20 weeks of gestation or from pre-pregnancy period [3]. The disease sometimes accompanied by proteinuria, failure of other organs or utero-placental dysfunction, so-called preeclampsia and regard as a severe-type of HDP [3]. Some HDP appears earlier than 34 weeks of gestation (early onset type), which results in low birth-weight infant and preterm birth both by placental dysfunction or by iatrogenic termination of pregnancy to rescue mothers.

HDP was traditionally regarded as an intractable pregnancy/delivery complication that was a direct cause of maternal death (mostly by brain stroke/eclampsia or renal failure). However, other more severe complications

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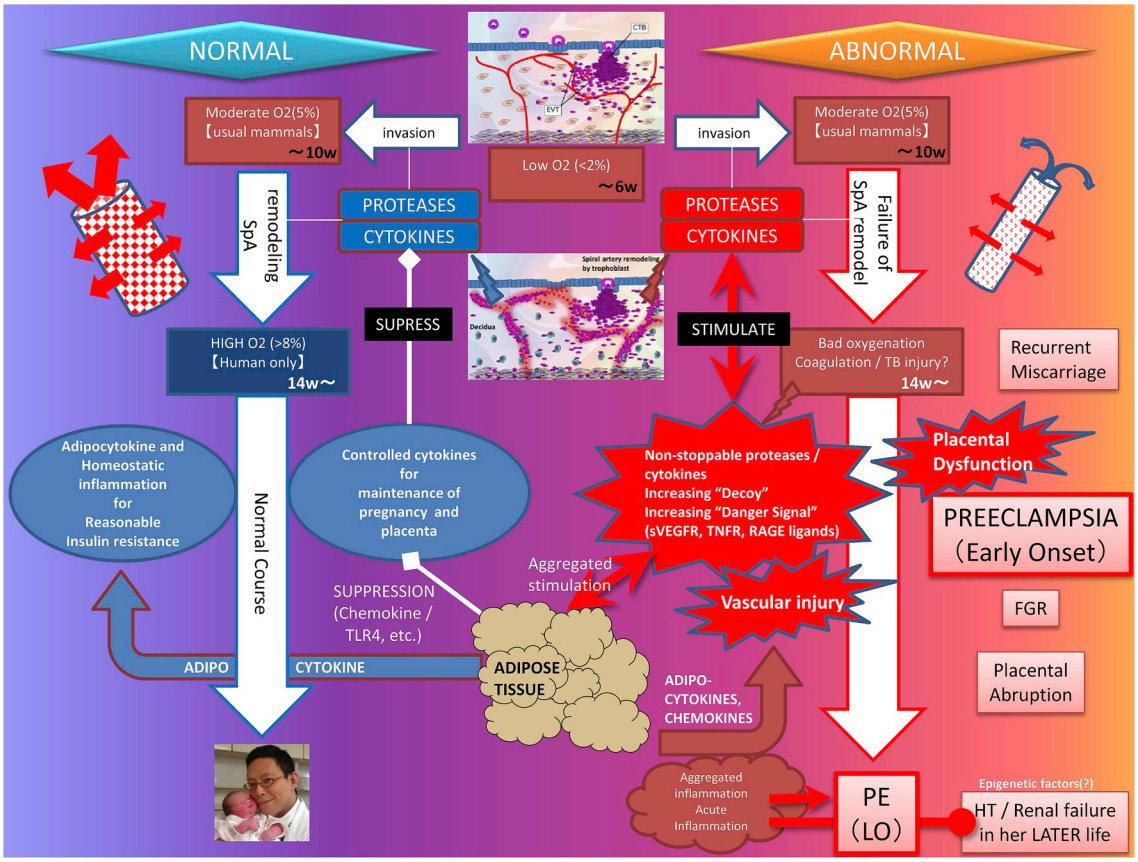

Fig. 1. Schematic diagram of the stages of a normal and abnormal (HDP and related complications) pregnant course. Left half showing fair placentation in normal pregnancy that with good spiral artery (SpA) remodeling, high oxygen concentration on placenta and controlled cytokine release. Right half is a pathway of complicated pregnancy that started with failed SpA remodeling, trophoblast (TB)/vascular injury and uncontrolled cytokine increase follow, which lead diseases in pregnancy. FGR; fetal growth restriction, PE; preeclampsia, LO; late onset-type, HT; hypertension.

are now known to be strongly related to HDP, including placental abruption, liver dysfunction (HELLP syndrome), cortical blindness, cardiomyopathy, and fetal growth restriction (FGR) [1]. Most of the known phenotypes of HDP classify it as a placental-origin disease, including cytokine and cell-based immune tolerance or conflict, circulating trophoblast debris and inflammation, and, most importantly, failed placentation with lack of spiral artery remodeling at 10–14 weeks of gestational age, which is related to subsequent ischemia [1–5]. Reduced blood flow and hypoxia/oxidative stress to the placenta and the fetus lead to an inflammatory cascade that exerts an effect on the maternal body, including to the vessels, kidney, placenta itself, and adipose tissue, and can also cause fetal damage with potential future health consequences (two-stage theory, Fig. 1). Thus, at present, HDP is not regarded as a single hypertensive complication occurring in the third trimester of pregnancy, but rather as a central disorder that can explain several unsolved pathological conditions throughout pregnancy. After this theory, early prediction of HDP by combined screening using uterine artery blood flow maternal and peripheral placental growth factor (PlGF) as markers has already proven to be successful for selective preventive therapy with low-dose aspirin, resulting in significant decrease of early-onset preeclampsia in a randomized controlled trial [6]. In addition, several basic and clinical studies on the role of PlGF or soluble FMS-like tyrosine kinase (sFlt)-1 in HDP or placental pathology have been published recently [7], which will not be further considered in this review.

Women who experience HDP have a significantly increased risk of developing cardiovascular diseases in later life, with a 4-fold increase of heart failure, 2.5-fold increase of coronary heart disease, and 1.8-fold increase of stroke [8]. In addition, neonates born after maternal HDP show an increased risk of developing cerebral palsy, especially in cases of preterm births, compared with infants born early from non-HDP mothers [9]. Indeed, growth restriction of a fetus and the subsequent catch-up growth may be considered as the origin concept of DOHaD research. Therefore, it is reasonable to consider that HDP is a multi-generation disease strongly related to the DOHaD concept, and the placenta may be representing the original and perhaps the most important site of this pathological conflict.

3. DOHaD and the placenta: what is already known?

As stated above, many placental biomarkers of preeclampsia flow into the maternal circulation and are already clinically used for disease prediction [7]. Most of these factors may be derived from the trophoblast surface during the early stage of pregnancy, including strong pro-inflammatory molecules in the so-called "danger signal" family [10]. Many molecules of placental origin in the healthy or complicated maternal circulation have been studied extensively. Our preliminary study showed that the expression level of high-mobility group box (HMGB)1, an example danger signal, was significantly increased in patients of HDP with severe features [11], which was linked to the development of pathological features in the third trimester of pregnancy. However, the effects of an increase of danger signal factors in the fetal circulation for mothers suffering from HDP are not yet known. Some studies focusing on HMGB1 in infants with other complications have provided some clues into this question, suggesting that these factors may have subsequent effects on infant health owing to a strong inflammatory response. Intra-amniotic infection/inflammation was associated with elevated amniotic fluid HMGB1 concentrations [12], and a high level of HMGB1 was observed in umbilical cord blood in cases of placental abruption and subsequent ischemia [13]. In addition, umbilical cord blood HMGB1 levels were reported to be significantly higher in women that had spontaneous and induced labor compared to non-laboring women [14]. Some other inflammatory molecules that are potentially

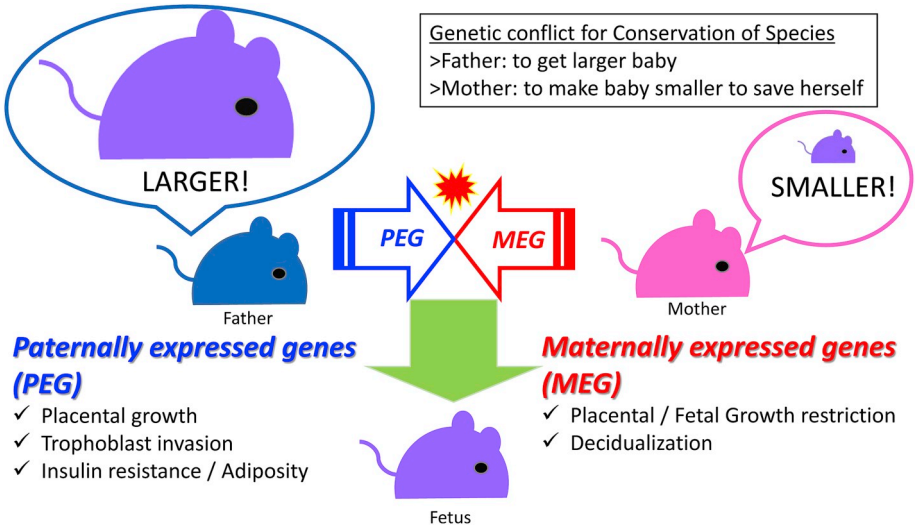

Fig. 2. Schematic representation of the paternal-maternal genetic conflict in HDP pathogenesis hypothesis. Paternal genes work to get more blood flow and nutrient from mother (left), but maternal genes work to protect herself via decidualization (right).

related to the DOHaD concept have also been studied in the context of pregnancy complications. We found that free fatty acid, which induces inflammation through Toll-like receptor 4 (especially in the adipose tissue), was increased in HDP patients [15]. Fatty acids are well-known factors in DOHaD studies, shown to be related to fetal risks for future development [16]. Moreover, the adipose tissue has recently been recognized as one of the largest sites of immunologic reactions, and genetic changes were also identified when applying our new method of whole-tissue culture with HDP serum [17]. The adipose tissue also distributes its native cytokines, known as adipocytokines, to modify the inflammatory response and insulin resistance in pregnancy, both in reasonably physiological or pathological (i.e., in HDP and/or gestational diabetes) manners [1]. Such alterations are similar to those observed in metabolic syndrome in non-pregnant subjects.

The direct effect of the placenta on fetal development may be related to hypoxic stress, which is supported by studies on cases of FGR [18], many of which are due to failed spiral artery remodeling and reduced blood flow, resulting in less oxygen and nutritional exchange. The pathophysiology of hypertensive disorder in patients suffering from hypoxia *in utero* is well studied, demonstrating the alteration of renal, vascular, and epigenetic factors [19]. Another review [20] suggested that oxidative stress, especially after fetal distress, may be largely related to mitochondrial damage and dysfunction.

Placental epigenetics has recently become a popular focus of research. This work has shown clear effects of environmental toxicants such as cigarette smoke or heavy metals in altering the DNA methylation and microRNA expression of the placenta [21]. However, even without these exposures or oxidative stress/hypoxia, hypermethylation was found in the placentas of cases of spontaneous preterm birth before 28 weeks gestation, and these higher rates of methylation were found to be maintained at cognitive function-related sites in 10-year-old offspring suffering from cognitive impairments [22]. In addition, a very recent study showed that the hypermethylation in FGR was related to inadequate maternal gestational weight gain [23]. A pathway search of placental and cord blood DNA methylation patterns in FGR cases further provided evidence that the epigenomic change passes through the placenta to exert direct effects on the fetus [24]. Another study demonstrated that imprinting genes (also see section 4 below) in the placenta were related with the neurobehavioral profiles of newborns [25]. Nevertheless, the epigenetic susceptibility of placenta-related pregnancy complications remains controversial. The general DNA methylation rate on the trophectoderm is lower than that of the inner cell mass [26], although the latest research in genome-wide methylation patterns suggests that the methylation rate in the placenta is higher than that of other organs, including the embryo or cord blood [Sato T., et al.: abstract P1.43. from IFPA 2018 Tokyo]. Thus, the placenta may be a sensitive organ for epigenetic change but might also have a protective function so as to not express these changes directly to the fetus.

4. Paternal-maternal genetic conflict on the placenta: new genetic insights into the feto-maternal interface

It has recently become clear that placental failure, especially the lack or absence of spiral artery remodeling, is the starting point of HDP, which subsequently distributes later toxic maternal circulating factors. As clearly indicated by Pijnenborg et al. [27], considering why “pre-eclampsia genes” were not eliminated in the evolutional process of the humans make attention to the fundamental factor contributing to disease onset at the feto-maternal interface. Recently, new information into the subtle genetic and epigenetic changes is coming to light in the present era of genome-wide sequencing, including research into many HDP-related genes (summarized in Ref. [28]), the role of DNA methylation on placental development [29], or non-coding microRNAs [30].

One such hypothesis that has been put forward to explain this unsolved problem is the so-called paternal-maternal genetic conflict [27,31]. From the paternal side of view, the fetus and placenta contain paternal-origin genes when they implant on the maternal uterine cavity, and the fetal trophoblast invades the decidua and remodels the spiral artery to obtain more blood flow from the mother for growth. From the maternal side, the uterine endometrium behaves protective in the pregnant state [27] that maintains its thickness and stabilizes itself (decidualization) so as to keep the fetus as small as possible [28,32], and thus avoid fatal blood loss at delivery (Fig. 2). A subsequent conflict then arises with maternal hypertension arising to provide more blood flow into the spiral artery remodeling-failed uterus. However, this hypothesis is controversial since it has not been confirmed whether the hypertension is derived from a fetal pathological demand or maternal self-sacrificing strategy. The same question arises with respect to the increase of maternal homeostatic insulin resistance, which is important for fetal growth and subsequent lactation, but can lead to gestational diabetes in certain cases.

Inspired by this hypothesis, one of the present authors conducted a systematic literature search [28] and found 140 significantly upregulated or downregulated genes in the HDP placenta, which were mainly involved in controlling pregnancy maintenance, metabolism, oxidative stress, cell cycle regulation, embryogenesis, implantation, immune modulation, and vascular function. Pathway analysis showed that 110 of these differentially expressed genes are related to cellular growth, and 30 were related to cellular growth restriction. In a follow-up study, Kobayashi [33] analyzed the down-regulated genes from this list and

found that those involved in regulating decidualization were likely to be decreased in the HDP placenta. This finding supports an earlier report showing that a defect of decidualization was associated with HDP and other pregnancy complications [34].

Another interesting finding from this analysis was that almost 60% of the HDP-related genes were located close to the imprinting cluster region on several chromosomes, including 1p31, 9q34, and 11p15.4 [33]. The alleles expressed for most of these genes could be easily defined in terms of their paternal or maternal origin [33], and a genetic conflict is considered to exist between these two groups: paternally expressed genes (PEG) contribute to placental growth, trophoblast invasion, and insulin resistance/adiposity, whereas maternally expressed genes (MEG) are related to placental/fetal growth restriction and decidualization [35,36]. Although the existence and contribution of sexual dimorphism on the placenta has been studied [37], the localization of pregnancy complications-related genes at imprinting clusters on placental chromosomes is not known, except in cases of rare "imprinting diseases" such as Beckwith-Wiedemann syndrome or intrauterine growth restriction, metaphyseal dysplasia, adrenal hypoplasia congenita, and genital anomalies (IMAGe) syndrome [38]. The mammalian placenta is the primary site of this genetic conflict, which is regarded as an important process in the history of the neocortical development and evolution of mammals [39]. Preliminary data from our ongoing study indicate that a few PEGs are decreased, whereas MEGs are increased in the placenta from HDP patients. These results support a role of a paternal-maternal genetic conflict in the pathogenesis of HDP. However, more epigenetic research is needed with consideration of the roles of PEGs and MEGs, including methylation anomalies.

5. Conclusions and prospects

A paternal-maternal genetic conflict may be the key to explaining fetal programing and a predictive adaptive response via the placenta in both successful and complicated pregnancies. It is now well recognized that placentation failure, especially lack of uterine spiral artery remodeling, and altered cytokines/danger signals are the main factors contributing to the pathophysiology of HDP. However, the first genetic events and factors leading to disease onset remain unclear. Recently, more research on pregnancy after oocyte donation is being performed owing to the increasing rate of the use of assisted reproductive techniques [40]. Although such research has thus far been limited to immunological differences (including decidual natural killer cells and HLA typing), this population provides an excellent opportunity for studies on genetic conflict. Understanding the genetic imbalance between paternal and maternal factors is expected to promote research in this field, focusing on the placenta as the key organ serving as the transfer platform.

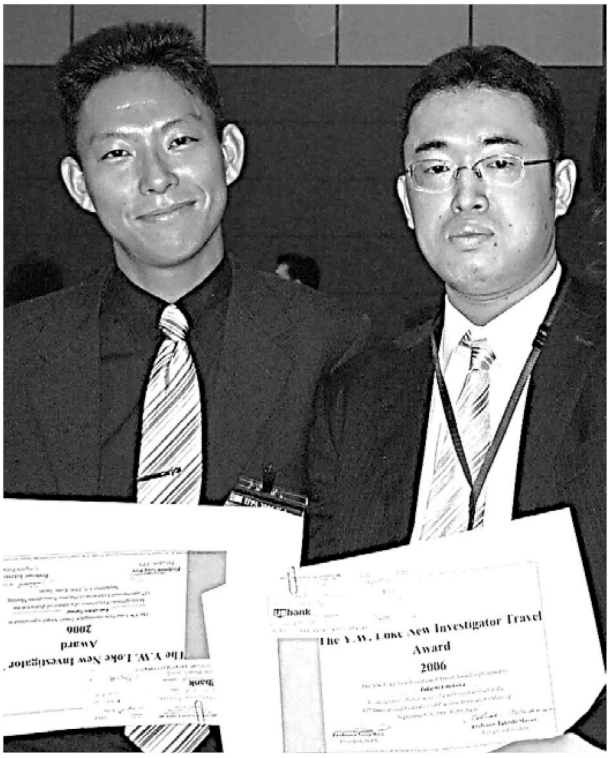

Fig. 3. Dr. Umekawa (right) and one of the present authors (Naruse) at the IFPA meeting of 2006 in Kobe, cerebrating winning the Y.W. Loke Young Investigators Award together.

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The presentation was dedicated to authors' friend Dr. Takashi Umekawa (Fig. 3) of Mie University, Japan, a skillful obstetrics consultant and researcher on HDP/insulin resistance in pregnancy and DOHaD, who passed away suddenly on February 24, 2018. May his soul rest in peace.

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