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Endothelial dysfunction and metabolic syndrome in preeclampsia: an alternative viewpoint

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ABSTRACT

Several clinical and basic science reports have elucidated partial aspects of the pathophysiology of preeclampsia and have led many authors to conclude that different "subtypes" of the disease exist. All these subtypes share the main clinical features of the disease and present additional characteristics that define different clinical phenotypes. Nevertheless, immunological alterations, endothelial dysfunction, and insulin resistance constantly characterize this syndrome. These aspects are intimately related at a molecular level; thus, we propose an alternative approach to explaining biologically the main intracellular processes that occur in preeclampsia and this may yield an insight into the pathogenesis.

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1. Introduction

Preeclampsia is a severe complication of human pregnancy that occurs in 3–5% of all pregnancies and may threaten maternal and fetal survival (Steegers et al., 2010). It is characterized by immunological alterations, systemic inflammation, endothelial dysfunction, and metabolic syndrome (Redman and Sargent, 2010; Redman et al., 2014). Preeclampsia presents with a pattern of typical clinical features (hypertension and proteinuria) and possible further manifestations (renal failure, HELLP syndrome, seizures), but the precise pathogenic mechanisms remain to be determined. Endothelial cell dysfunction is a hallmark of the pathogenesis of the diseased (Roberts et al., 1989). The clinical syndrome develops from an altered balance between factors produced by the placenta and maternal reaction to them. Immune responses to trophoblast invasion in the early stages (maternal immune adaptation to fetal alloantigens) promote systemic nonspecific inflammation that can lead to the development of the disease later in pregnancy (Redman and Sargent, 2010). Epidemiological studies suggested a definite paternal-specific risk of developing preeclampsia (Robillard et al., 1994). In fact, maternal exposure to paternal sperm and seminal plasma and the adaptation to them seem to play a role in the unbalanced immunoregulation at the maternal/placental interface promoting an inadequate trophoblast invasion of the placenta bed (Burton and Jauniaux,

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2004). Subsequently, an imbalance of circulating angiogenic factors occurs and results in maternal endothelial dysfunction, which induces the clinical syndrome (Mutter and Karumanchi, 2008). Interestingly, the unique immune environment at the maternal/fetal interface may contribute to the angiogenic balance necessary to maintain a healthy pregnancy (Hanna et al., 2006). The decidual NK cells that populate the interface are in direct contact with the invasive placental trophoblasts. These NK cells produce angiogenic factors that may be crucial for remodeling the spiral arteries and creating the appropriate angiogenic environment at the placental bed. Although it is still unclear how the endothelial dysfunction observed in preeclampsia relates to the long-term risk of cardiovascular disease there is now some evidence that suggests that endothelial alterations might persist after pregnancy and increase the risk of cardiovascular diseases in women who have suffered from preeclampsia (Williams, 2011; Ahmed et al., 2014). In fact, large retrospective cohort studies have found that preeclampsia is associated with a 3- to 7-fold risk of cardiovascular disease later in life and the pathogenesis is based on genetic determinants shared with metabolic syndrome and inflammation (Giguère et al., 2012; Östlund et al., 2013).

An exacerbation of a metabolic syndrome that takes place physiologically during normal pregnancy has been reported in preeclamptic women (Seely and Solomon, 2003; Catalano, 2010). Kaaja et al. (1999) have reported that preeclamptic women have 37% lower insulin sensitivity and women with a pre-gestational metabolic syndrome are more likely to develop preeclampsia during pregnancy (Emery et al., 2005; Ness and Sibai, 2006). This applies not only to obese women, who are already at a triple risk of developing the disease (Ilekis et al., 2007), as the metabolic syndrome with insulin resistance can occur in non-obese subjects (Oda, 2008). Notably, the metabolic syndrome has long been associated with late-onset preeclampsia, while recent studies have reported that the prevalence of metabolic syndrome postpartum is twice as high in women who had early-onset compared with late-onset preeclampsia (Stekkinger et al., 2009).

Although several aspects of the pathophysiology of preeclampsia have been partly elucidated, a deep comprehension of the mechanisms of its pathogenesis and how they interact is still lacking. The main clinical features of preeclampsia; namely, endothelial dysfunction and metabolic syndrome, have always correlated individually with the inflammatory response that occurs in preeclampsia (Redman and Sargent, 2010), while they may be derived from the convergence of different signaling pathways that originate from immunological stimuli, inflammation, and metabolic alterations. Here, we propose an alternative relationship among these aspects that involves at the molecular level endothelial and metabolic biomarkers of the syndrome.

2. Angiogenic proteins

Many endothelial-derived vasoactive mediators have been investigated in preeclamptic women in the past decade. Two circulating proteins; namely, soluble fms-like kinase 1 (sFlt-1) and placental growth factor (PlGF), have gained interest in the past few years and have been shown to contribute to endothelial dysfunction in preeclampsia (Maynard et al., 2003; Levine et al., 2006). Antiangiogenic sFlt-1 is a nonmembrane-bound alternative splice form of the vascular endothelial growth factor (VEGF) receptor Flt-1. It has been found to be increased before the onset of clinical preeclampsia, along with a decrease in the free bioactive proangiogenic PlGF. The alternative splice form associated with preeclampsia includes part of intron 14 (Sela et al., 2008). The increase in sFlt-1 and decreased PlGF correlate with the severity of the disease (Powe et al., 2011) and the increase in the sFlt-1 to PlGF ratio may be a good predictor of the disease (Thadhani et al., 2004a; Noori et al., 2010). An appropriate angiogenic balance may be a key regulator of the disease, although it is unknown what triggers the antiangiogenic state. Other antiangiogenic proteins, such as soluble endoglin (Eng), have also been shown to contribute to the development of preeclampsia. The abnormal production of sFlt-1 and soluble Eng induces endothelial dysfunction by inhibiting VEGF/PlGF and TGFβ signaling pathways respectively (Romero and Chaiworapongsa, 2013). The longitudinal assessment of maternal serum levels of angiogenic factors as early biomarkers for the prediction of preeclampsia have failed to provide sufficient evidence for a clinical use, although good accuracy was found in early-onset preeclampsia (before 34 weeks' gestation) (Myatt et al., 2013). This can be due to evidence that preeclampsia is a heterogeneous disease with different pathophysiological pathways (Rana et al., 2014).

3. Insulin resistance and D-chiro-inositol in preeclampsia

The metabolic syndrome that occurs during preeclampsia is typically associated with insulin resistance and endothelial dysfunction (Salzer et al., 2014; Scioscia et al., 2014). Insulin resistance is defined as impairment of the action of insulin on glucose and lipid metabolism, while endothelial dysfunction is defined as inadequate endothelial-mediated vasodilation. Recently, Founds et al. (2011) have reported that insulin resistance is higher as inflammation increases in preeclampsia. Furthermore, insulin resistance and endothelial dysfunction represent early events in individuals at high risk of developing cardiovascular disease later in life (Fraser et al., 2012).

In the past decade, interest in D-chiro-inositol phosphoglycan (DCI) in the study of the pathophysiology of preeclampsia has increased (Scioscia et al., 2011). DCI is an insulin mediator that derives from the intracellular epimerization of myo-inositol and promotes many insulin-like effects, modulates insulin action, and enhances insulin sensitivity (Larner, 2002). Increased levels of the lipidic form of DCI were reported even before the onset of clinical preeclampsia in maternal urine specimens (Williams et al., 2007; Paine et al., 2010; Dawonauth et al., 2014). Placental studies demonstrated that DCI content was consistently higher in preeclampsia than in matched controls (Kunjara et al., 2000) and the assessment of placentas of early-onset preeclamptic cases showed higher content of

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