Human Immunology (2007) 68, 668–674

journal homepage: www.elsevier.com/locate/humimm

Immunogenetics of pregnancy: Role of a 14-bp deletion in the maternal HLA-G gene in primiparous pre-eclamptic Brazilian women

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Received 2 March 2007; received in revised form 13 April 2007; accepted 24 May 2007

KEYWORDS
HLA-G polymorphism;
Pre-eclampsia;
Immunomodulation

Summary The etiology and pathogenesis of pre-eclampsia (PE) involve a combination of maternal–fetal genetic and immunologic factors. The immunologic maladaptation theory of PE predicts that the maternal immune system does not tolerate the semi-allogeneic fetus. Human leukocyte antigen-G (HLA-G) is expressed in some types of immune cells as well as in the fetal–maternal interface by trophoblasts, playing an immunoregulatory role. Here we have evaluated a 14-bp deletion polymorphism in the 3′-untranslated region of exon 8 of HLA-G gene in pregnant PE women and controls. HLA-G genotypes in both control and PE women were in Hardy-Weinberg equilibrium. The healthy pregnant and PE women had similar genotype frequencies ($p = 0.789$). This was similarly observed when PE women were subgrouped accordingly to severity of disease ($p = 0.646$). However, the primiparous PE women presented a tendency toward higher frequency of the 14-bp deletion allele (0.442) compared with the primiparous healthy women (0.286), $p = 0.09$. Our data suggest that the maternal 14-bp deletion of HLA-G is not associated with the risk for PE but that it could affect the development of PE in primiparous women.
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Introduction

Pre-eclampsia (PE) is a systemic disorder of unknown origin that is characterized by abnormal vascular response to placentation, increased systemic vascular resistance, enhanced platelet aggregation, activation of the coagulation cascade, and endothelial cell dysfunction [1]. The etiology and pathogenesis of PE involve a combination of maternal-fetal genetic and immunologic factors. The disorder is heterogeneous and pathogenesis can differ in women according to the presence of different risk factors. Pathogenesis of PE in pri-

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doi:10.1016/j.humimm.2007.05.006

ABBREVIATIONS

HLA-G	human leukocyte antigen-G
IL-10	interleukin-10
PE	pre-eclampsia
TH1	T helper lymphocyte type 1
TH2	T helper lymphocyte type 2
UTR	untranslated region

miparous women may differ to that in women with pre-existing vascular disease, multifetal gestation, diabetes mellitus, or previous pre-eclampsia events [2,3]. Women with PE are usually diagnosed with hypertension and associated proteinuria. PE can be serious if severe hypertension is associated with proteinuria or if hypertension is associated with severe proteinuria (≥5 g per day) [4,5]. In general, maternal and perinatal outcomes are usually favorable in women with mild PE developing beyond of 36 weeks of gestation. In contrast, maternal and perinatal morbidities and mortalities are increased in women who develop the disorder before the 33th week of gestation [5-7]. PE is usually regarded as a disease of first pregnancy.

The immunologic maladaptation hypothesis of PE predicts that the maternal immune system does not tolerate the semiallogeneic fetus. During pregnancy, the maternal immune system is in close contact with cells and tissues of the semiallogeneic fetus. Therefore, there must be specific mechanisms engaged in modulating the maternal immune system to prevent the fetus rejection. Women with healthy pregnancies tend to present with a Th2 type of immune response, whereas a Th1 type response is incompatible with a successful pregnancy and plays a role in certain complications such as PE development [8-12]. Human leukocyte antigen-G (HLA-G) is a nonclassical HLA class Ib molecule that is predominantly expressed in the fetal-maternal interface and plays an important role during implantation and maternal acceptance of the fetus. HLA-G mRNA has been detected in many different tissues, whereas HLA-G protein expression is limited to a few specific cells such as trophoblasts in placenta, monocytes, lymphocytes, and thymus [13-15]. Some immunologic interactions can contribute to fetal maintenance. Expression of HLA-G by trophoblasts inhibits activation of maternal T cells, natural killer (NK) and antigen-specific CTL cytolysis via specific receptors [16-19], and IL-10 secreting cells may stimulate the HLA-G expression [20]. Interestingly, some effectors CD4+ and CD8+ T lymphocytes acquire immunosuppressive HLA-G1 from antigen-presenting cells (APCs) and reverse their function from effectors to regulatory cells [21]. Recently Fanchin *et al.* reviewed the possible relationship between HLA-G and human embryo implantation, exploring the HLA-G expression on human preimplantation embryos and in the endometrium, as well as its levels in embryo culture supernatants and circulating maternal blood [22]. HLA-G has few polymorphic alleles and shows a limited pattern of expression, contrasting to the highly polymorphic HLA class Ia and II antigens [15,23-32]. A very interesting variation of HLA-G involves a 14-bp deletion/insertion polymorphism in the 3′UTR of the HLA-G gene located at position 3741 at exon 8. The 14-bp sequence at the beginning of exon 8 is suggested to be responsible for the alternative splicing of the HLA-G transcript. This 14-bp polymorphism has been associated with HLA-G isoforms that lack 92 base sequences in the first part of exon 8 (3′UTR) [33]. During mRNA processing, this sequence functions as a cryptic branch point for mRNA splicing and is thus more stable in nature [34,35]. However, the 14-bp deletion causes the retention of 92 bases in the mature transcript, resulting in an unstable transcript. The 14-bp deletion/insertion polymorphism may influence both the HLA-G isoform splicing patterns and HLA-G mRNA stability. This may change the HLA-G function and could be of pivotal importance in certain pregnancy complications like PE [35,36]. The allele +14 bp has been associated with lower levels of soluble HLA-G and was implicated in the development of PE and recurrent abortions [35,37,38]. Several studies have been suggested the importance of the maternal HLA-G expression during cleavage embryo development and during the course of pregnancy. Yao *et al.*described a disparity between HLA-G mRNA isoforms and protein expression in embryos. They suggested that in some stage embryos, this difference might be caused by HLA-G protein remaining from maternal oocyte stores produced before embryonic genome activation. Thus HLA-G expressed at this stage may be more a marker of oocyte rather than embryonic quality [39]. In addition, Menezo *et al.* reported that the levels of secreted soluble HLA-G protein are higher than the capacity proposed for soluble HLA-G release by the embryo, so the signals secreted by the embryos are not in the order of magnitude of estimated HLA-G protein concentrations [40]. These findings shed some light on the contribution of the maternal HLA-G protein to a successful pregnancy. In this case-control study, we analyzed the maternal 14-bp HLA-G polymorphism, investigating both allelic and genotypic frequencies in Brazilian women who developed PE. The hypothesis of immune maladaptation in PE was studied here, evaluating the importance of maternal HLA-G genotype during a successful pregnancy.

Subjects and methods

Individuals

The patients were recruited at the Maternity Unit of at public hospital in Southern Brazil (Hospital Nossa Senhora Conceição, Porto Alegre). We identified 162 healthy pregnant women with uncomplicated pregnancies (controls) and 157 pregnant with PE. The inclusion criteria for selecting controls included: no rise in blood pressure, no hypertension or proteinuria, similar age (healthy women 28.08 years ± 7.37 years, and PE women 30.32 ± 7.46 years), no biologic relationship and a delivery date as close as possible to the delivery date(s) of the matched patient group. Controls were followed up for at least 3 months after delivery. If hypertension and/or proteinuria were observed during this follow-up period, this specific control individual was excluded. Pre-eclampsia was defined as the presence of hypertension and proteinuria. Hypertension is characterized by blood pressure of ≥140 mm Hg (systolic) or at least 90 mm Hg (diastolic), on at least two occasions and 4-6 hours apart after the 20th week of gestation in women known to be normotensive previously [5,41]. Proteinuria is defined as an excretion of ≥300 mg of protein every 24 hours. If 24-hour urine samples were not available, proteinuria was defined as a protein concentration of 300 mg/l or more (≥1 + on dipstick) in at least two random urine samples

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