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Journal of Reproductive Immunology 77 (2008) 100–108

JOURNAL OF REPRODUCTIVE IMMUNOLOGY

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The human tumor-associated antigen RCAS1 in pregnancies complicated by pre-eclampsia

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Received 14 March 2007; received in revised form 26 April 2007; accepted 16 May 2007

Abstract

The human tumor-associated antigen RCAS1 (receptor-binding cancer antigen expressed on SiSo cells) is considered to play a role in the escape of tumor cells from immune surveillance and, at the same time, participates in the inhibition of the maternal immune response during pregnancy. The aim of our study was to investigate the expression of tumor-associated RCAS1 protein in the placenta and amniotic membranes and to assess and compare its concentration in amniotic fluid, maternal and cord blood sera in pregnancies complicated by pre-eclampsia. Samples were obtained from women with pre-eclampsia ($N = 9$), pre-eclampsia with IUGR ($N = 4$), normotensive IUGR ($N = 7$) and healthy term controls ($N = 25$) after delivery. Placentas were studied by immunohistochemistry, Western blot analysis and real-time (RT)-PCR. For assessment of RCAS1 protein concentrations in biological fluids, ELISA was performed. RCAS1 mRNA expression in the placentas of pre-eclamptic patients was significantly lower than in controls ($p < 0.01$). The maternal blood serum RCAS1 protein concentration in the pre-eclampsia cases was also significantly lower than in controls ($p = 0.0207$). The other study groups did not differ significantly. This study reveals the possible role of the RCAS1 protein in the development of pre-eclampsia through an immunological pathway.
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Keywords: IUGR; Maternal blood; Placenta; Pre-eclampsia; RCAS1

1. Introduction

Pre-eclampsia is a potentially dangerous complication of the second half of pregnancy, labor or the early period after delivery, and is characterized not only by hypertension but also a high level of proteinuria, edema and other systemic changes. Pre-eclampsia occurs in 5–8% of pregnancies. In the past few years, two broad categories of pre-eclampsia have been proposed: placental pre-eclampsia and maternal pre-eclampsia, pointing to the primary source of the disease. Mixed presentations, combining maternal and placental contributions, are common (Redman and Sargent, 2005). The tumor-associated antigens that can be recognized by the immune system might have a crucial role in the development of pre-eclampsia. Recent studies have defined the expression of tumor-associated proteins in trophoblastic tissues (Jeschke et al., 2006) and shown that a significant imbalance in expression of tumor-associated proteins could lead to early apoptosis in pre-eclampsia (Heazell et al., 2005). On the other hand,

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0165-0378/$ – see front matter © 2007 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.jri.2007.05.001

with respect to systemic inflammation, there is substantial evidence to support the concept that pre-eclampsia develops when the normal inflammatory response of pregnancy is exaggerated (Sargent et al., 2006; Crocker, 2007). Moreover, it has been reported that human T and NK cells express the RCAS1 receptor at a high level after being activated, and that RCAS1 (the human tumor-associated antigen) inhibits proliferation and induces apoptotic cell death of receptor-positive immune cells (Nakashima et al., 1999). These findings led to our interest regarding RCAS1 protein in connection with pre–eclampsia.

The tumor-associated antigen RCAS1 was defined by its immunoreaction with the 22-1-1 monoclonal antibody (mAb), which was raised by immunization of mice with the human uterine cervical adenocarcinoma cell line SiSo (Sonoda et al., 1996). The gene product was termed 'receptor-binding cancer antigen expressed on SiSo cells' (RCAS1) and is identical with the estrogen-responsive protein EBAG9 (estrogen receptor-binding fragment-associated gene9) which is located on chromosome 8q23 (Nakashima et al., 1999; Ikeda et al., 2000). RCAS1 is a predominantly Golgi-localized membrane protein (Reimer et al., 2005). It is a homodimer with molecular weight of 25 kDa. RCAS1 acts as a ligand for a putative receptor present on various human cell lines and normal peripheral lymphocytes such as T, B and NK cells. The receptor expression is enhanced by activation of lymphocytes. RCAS1 inhibits the *in vitro* growth of receptor-expressing cells and induces apoptotic cell death, suggesting its involvement in the immune escape of tumor cells (Nakashima et al., 1999). This protein is involved also in regulating apoptosis of erythroid progenitor cells, and might have a critical role in erythropoesis (Matsushima et al., 2001). The RCAS1 protein is expressed in different human tissues and organs, including female organs as well (Kawano et al., 2005; Wicherek et al., 2005a). It has been widely studied in tumor malignancies as a biomarker associated with poor prognosis of cancers (Akahira et al., 2004; Kaku et al., 1999; Chatterjee et al., 2006; Sonoda et al., 2003).

There have been several studies investigating RCAS1 expression and immune tolerance during pregnancy (Ohshima et al., 2001; Wicherek et al., 2005b,c), stillbirth (Wicherek et al., 2005d), the process of placental detachment (Wicherek et al., 2006) and comparative analyses of the normal placenta and neoplasm (Wicherek et al., 2003). The aim of the present study was to assess the association between RCAS1 protein in the placenta and pre-eclampsia.

2. Methods

2.1. Patients

For this investigation we selected 45 patients with singleton pregnancies. None had chronic or gestational hypertension, renal disease or stillbirth. Out of the 45 patients, 9 women had pregnancies complicated by pre-eclampsia, 4 had pre-eclampsia with intrauterine growth retardation (IUGR), 7 women, normotensive IUGR; and all delivered by either cesarean section or induction of labor (using intracervical Foley catheter followed by intravenous oxytocin infusion). The control group consisted of 25 healthy women who delivered at 38–40 weeks of gestation. Pre-eclampsia was defined by hypertension with a systolic blood pressure of ≥140 mmHg and/or diastolic blood pressure of ≥90 mmHg in association with proteinuria (24 h urinary protein exceeding 300 mg per 24 h or persistent 30 mg/dL (1 + dipstick) in random urine samples), with or without edema. IUGR was defined by the presence of ultrasonographic signs (biparietal diameter below the 10th percentile and abdominal circumference below the 5th percentile) on admission and by birth weight below the 10th percentile according to Japanese standards for birth weight and gestational age (Shinozuka et al., 1987). Asymmetrical type of IUGR was determined after delivery. The main characteristics and pregnancy outcome of the study groups are given in Table 1.

2.2. Sample preparation

After approval by the local ethics committee of the Department of Obstetrics and Gynecology, Osaka University Graduate School of Medicine, informed consent was obtained from each patient. We collected amniotic fluid, maternal peripheral blood and umbilical cord blood from women who developed pre-eclampsia ($N = 9$), pre-eclampsia with IUGR ($N = 4$) or normotensive IUGR ($N = 7$) and 25 healthy controls. Thirty-six samples of placenta and amniotic membranes were obtained from women with pre-eclampsia ($N = 7$), pre-eclampsia complicated by IUGR ($N = 4$), normotensive IUGR ($N = 7$) or the controls ($N = 18$). For immunohistochemistry, a portion of placenta and amnion were fixed in 10% formaldehyde neutral buffer. The rest of the placental and amniotic tissue was frozen in liquid nitrogen and stored at −80 °C until use. Amniotic fluid samples were collected and centrifuged at room temperature at $1200 \times g$ for 20 min. Supernatants were stored at −80 °C before measurement of the protein concentration. Blood sam-

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