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Lymphokine-activated killer cells induced from decidual lymphocytes reduce the angiogenic activity of trophoblasts by enhancing the release of soluble fms-like tyrosine kinase-1 from trophoblasts: An implication for the pathophysiology of preeclampsia

Kaya Matsubara, Takeshi Nagamatsu, Tomoyuki Fujii*, Shiro Kozuma, Yuji Taketani

Department of Obstetrics and Gynecology, Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, 113-8655 Japan

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Abstract

T helper (Th)1 cytokine-predominating status and compromised placental vasculature is thought to be central to the pathogenesis of preeclampsia. However, it remains to be clarified how these two phenomena relate to each other. We have reported that lymphokine-activated killer (LAK) cells induced from decidual mononuclear cells (DMCs) with interleukin (IL)-2 expressed in preeclamptic placenta reduced the angiogenic activity of cytotrophoblasts (CTs). The objective of this study was to examine how LAK cells reduced the angiogenic activity of CTs. We investigated the angiogenesis-related molecules released from cultured CTs obtained from first trimester placenta that had been pretreated with either non-activated DMCs or LAK cells from DMCs. The amounts of vascular endothelial growth factor (VEGF), placenta growth factor (PlGF) and their antagonist, soluble fms-like tyrosine-kinase-1 (sFlt-1) released in CT culture media were measured using ELISA. CTs pretreated with LAK cells released more sFlt-1 compared with those pretreated with non-activated lymphocytes, and CTs pretreated with non-activated lymphocytes released more sFlt-1 compared with those without pretreatment. The release of total VEGF and free PlGF from CTs was not altered by pretreatment

* Corresponding author. Tel.: +81 3815 5411; fax: +81 3816 2017.
E-mail address: fujiit-tky@umin.ac.jp (T. Fujii).

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with DMCs. Thus, in preeclamptic placenta, LAK cells induced from DMCs by co-existing IL-2 may react to the invading CTs and enhance the release of sFlt-1 from CTs without any change of VEGF or PlGF secretion. This might result in the reduction of actual angiogenic potential of the VEGF system in decidua and the placental vascular system might be compromised, which may lead to the development of preeclampsia.

Keywords: Angiogenesis; Interleukin-2; Preeclampsia; Soluble fms-like tyrosine kinase-1; Th1 cytokine; Trophoblasts

1. Introduction

Recent emerging evidence suggests that the disruption of immune regulation during pregnancy may be involved in the pathophysiology of preeclampsia. For instance, the T helper (Th)1/Th2 balance shifts to Th1 predominating status in preeclampsia, whereas Th2 cytokines predominate and suppress Th1-type immune reactions in normal pregnancy (Wegmann et al., 1993; Darmochwal-Kolarz et al., 1999; Saito et al., 1999), although a recent report showed that the simple classical Th1/Th2 theory might be invalid in the maintenance of pregnancy (Chaouat et al., 2002). In particular, the serum interleukin (IL)-2 levels are elevated in preeclamptic women even before the manifestation of the symptoms of preeclampsia (Hamai et al., 1997a) and IL-2 is present in decidual tissue obtained from preeclamptic patients, but not from normal pregnant women (Hara et al., 1995). These findings reflect the activated state of decidual immune cells, point to a possible immune activation in the decidua of preeclamptic patients, and might have pathogenic relevance to preeclampsia.

Growth of the placenta requires extensive angiogenesis to accomplish an adequate vascular structure. Several recent lines of evidence have suggested the essential roles played by cytotrophoblasts (CTs) in constructing placental vasculature. Specifically, angiogenic growth factors, such as vascular endothelial growth factor (VEGF; Jackson et al., 1994; Clark et al., 1996, 1998; Vuckovic et al., 1996) and placenta growth factor (PlGF; Khaliq et al., 1996) are suggested to act locally and control the vascular remodeling in placenta. On the other hand, aberration of placental vasculature is thought to be central to the pathogenesis of preeclampsia (Meekins et al., 1994; Brosens et al., 2002; Granger et al., 2002). We have reported that pretreatment of trophoblasts with lymphokine-activated killer (LAK) cells induced by decidual lymphocytes with IL-2 selectively reduced the angiogenic activity of the culture medium of trophoblasts (Hamai et al., 1997b). Thus, taken together with the presence of IL-2 in preeclamptic deciduas and the fact that IL-2 enhances the cytotoxic activity of decidual lymphocytes (Parhar et al., 1989; King and Loke, 1990; Starkey, 1991; King et al., 1992; Saito et al., 1993), it is intriguing to speculate that LAK cells might be induced from decidual lymphocytes in preeclampsia. LAK cells may interact with CTs and reduce the angiogenic activity of CTs, resulting in the aberrant vasculature of the placenta, which leads to the development of preeclampsia. However, it remains to be clarified how LAK cells reduce the angiogenic activity of CTs.

Recently, an increasing number of studies have shown the elevated concentration of soluble fms-like tyrosine-kinase-1 (sFlt-1), which is a potential antagonist for both VEGF