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CD9 suppresses human extravillous trophoblast invasion

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Introduction

During human placentation, trophoblasts proliferate and differentiate into an extravillous trophoblast (EVT) in the anchoring villi. Then, EVT invades the maternal decidua and reconstructs maternal spiral arteries, reducing arterial contractility to maintain adequate maternal blood flow into the intervillous spaces [1]. Various biologically active molecules, such as several growth factors [2, 3] and proteinases [4-6], and cell-cell and/or cell-extracellular matrix interactions mediated by adhesion molecules, such as cadherins and/or integrins [7], have been proposed to be important to regulate EVT invasion. The Eph-ephrin system was also reported to be involved in placentation by EVT [8, 9]. Recently, the interaction between EVT and decidual immune cells, especially uterine natural killer cells, has been proposed to regulate EVT invasion [10]. In contrast to malignant cells, EVT invasion is confined spatially to the uterus and temporally to early pregnancy. However, the molecules described above cannot fully explain the spatiotemporal development and differentiation of EVT.

Previously, we reported that a cell surface molecule, CD9, was weakly expressed on EVT in the cell columns of first trimester placentae and highly expressed on EVT in the basal plate of placentae in the second and third trimesters and in the chorion laeve in the fetal membrane of term placentae [11]. CD9 was initially considered to be specific for acute lymphoblastic leukemia cells [12]. This antigen was also expressed on a variety of tumors and normal human cells, including pre-B cells, activated T cells, and Schwann cells [13-15]. It has been shown that anti-CD9 mAbs induce the migration of Schwann cells [15] and endothelial cells [16], and regulate the adhesion of pre-B cells to bone marrow fibroblasts [17]. CD9 was also reported to play a critical in sperm-egg fusion in fertilization [18, 19], suggesting the involvement of CD9 in cell adhesion, migration and cell fusion. Although the precise physiological role of CD9 is still unknown, CD9-targeted therapy for cancer was recently proposed [20].

By invasion assay, the binding of anti-CD9 mAb (ALB-6) to CD9 enhanced the number of invaded BeWo cells without affecting cell proliferation. Although these findings suggest the involvement of CD9 in human trophoblast invasion [21], this did not provide direct evidence because