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Differential cellular expression of LIGHT and its receptors in early gestation human placentas

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Abstract

LIGHT (homologous to *l*ymphotoxins, exhibits *i*nducible expression, competes with herpes simplex virus *g*lycoprotein D for HVEM, a receptor expressed by T lymphocytes) is an apoptosis-inducing member of the tumor necrosis factor family of ligands. Messenger RNAs encoding LIGHT and its receptors, lymphotoxin-β receptor (LTβR), decoy receptor-3 (DcR3) and herpes virus entry mediator (HVEM), are present in first trimester and term placentas. Proteins have been localized to specific cells in term but not earlier gestation placentas. Here, we have studied LIGHT and its receptors in early (6–7 weeks) and early-to-middle (8–13 weeks) gestation using immunohistology. Notable cell-specific, gestation-related features were identified. LIGHT and two of its receptors, a membrane-bound receptor that mediates apoptosis (LTβR) and a soluble receptor that interferes with LIGHT signaling (DcR3), were present in syncytiotrophoblast and cytotrophoblast cells in all samples but were detected in placental stromal cells only at week 8 and thereafter. HVEM, a membrane-bound receptor that protects against apoptosis, was expressed only on syncytiotrophoblast. These observations suggest that the LIGHT system may regulate early to middle stages of placental development via cell-specific, temporally programmed expression of the ligand and its receptors, and may also assist in preserving placental immune privilege.

Keywords: Human; LIGHT; Placenta; LIGHT receptors; TNFSF14; TNF superfamily

1. Introduction

Human placental development and the signaling systems that drive trophoblastic differentiation remain poorly understood despite the fact that abnormalities of placentation contribute to pathologies of pregnancy and fetal loss (Jauniaux and Burton, 2005). The tumor necrosis factor (TNF) gene family is believed to participate in these processes via regulation of genes involved in programmed cell death as well as other critical placental functions such as hormone production (Hunt et al., 1996).

TNFα, LIGHT and lymphotoxins (LT) are among the apoptosis-inducing ligands that are transcribed and translated in human placentas (Chen et al., 1991; Phillips et al., 2001; Gill et al., 2002; Gill and Hunt, 2004). The network connections identified to date among LIGHT, TNFα and LT, as well as their receptors, are illustrated in Fig. 1 (adapted from Ware, 2005). Sharing of receptors is a notable feature of this group of cytokines. Of the three ligands, LIGHT is the least well studied. LIGHT has three receptors, lymphotoxin-beta receptor (LTβR), decoy receptor three (DcR3) and herpes virus entry mediator (HVEM). The LTβR is a membrane-bound

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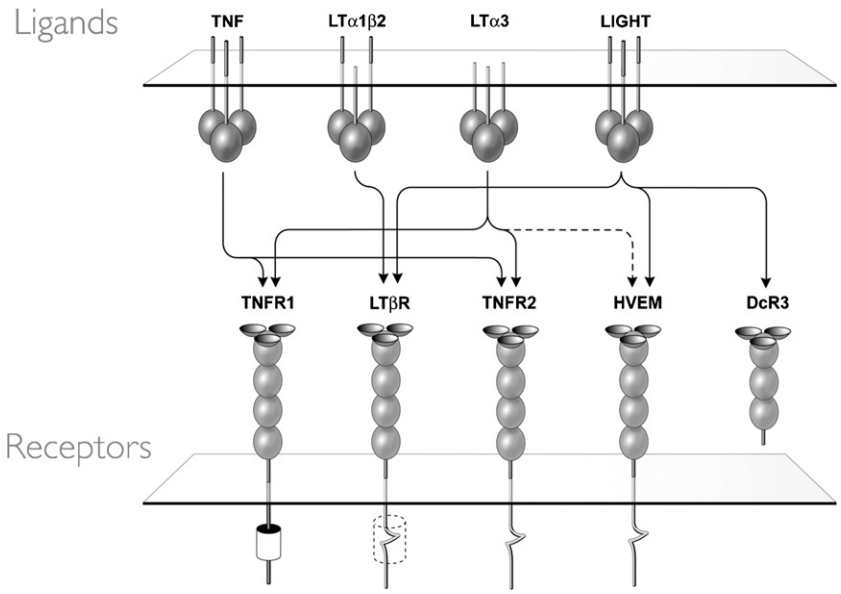

Fig. 1. Cartoon illustrating ligand receptor pairs in the LT/LIGHT/TNF network. Note that receptors may bind more than one ligand. TNF-R1 contains a death domain (cylinder), and other receptors are capable of mediating cell death or not by using alternative pathways (squiggle). Adapted from Ware et al. (2005).

receptor that transduces a signal resulting in apoptosis (Harrop et al., 1998; Rooney et al., 2000; Mauri et al., 1998; Browning et al., 1997). DcR3 is a soluble receptor that competitively inhibits LIGHT signaling through both LTβR and HVEM (Yu et al., 1999; Zhang et al., 2001). HVEM, a membrane-bound receptor, signals upregulation of NFκB-dependent gene expression and exerts a protective effect (Kwon et al., 1997; Harrop et al., 1998; Mauri et al., 1998; Tamada et al., 2000a,b).

Human placentas at both early and late stages of gestation contain mRNAs encoding LIGHT and its three receptors, as shown in our earlier studies (Phillips et al., 2001; Gill et al., 2002). Experimental evidence for LIGHT-associated autocrine death pathways in placenta is limited at present to our in vitro study of cytotrophoblast cells taken from term placentas (Gill and Hunt, 2004). The cytotrophoblast cells were shown to undergo apoptosis when incubated with LIGHT (Gill and Hunt, 2004). This occurred only when IFN-γ, a cytokine also present in placentas (Paulesu et al., 1994), was included in the culture medium. Together, these cytokines bypass cIAP-2 (cellular inhibitor of apoptosis-2), a regulator of caspase-3 (Gill and Hunt, 2004). Thus, the LIGHT system might participate in programmed cell death or perform other functions at both stages of gestation (Harrop et al., 1998; Rooney et al., 2000; Tamada et al., 2000a,b, 2002; Wang et al., 2004; Watts, 2005). In our earlier study (Gill et al., 2002), analysis of ligand and receptor proteins was conducted only on term placentas. Because major events in placental development take place earlier in gestation that might be influenced by LIGHT and its network partners, TNFα and LT, the goal of the current study was to establish the cellular localization of the LIGHT ligand/receptor system and identify any temporal changes in expression that occur during early-to-middle gestation.

2. Materials and methods

2.1. Reagents

All reagents were obtained from Sigma Chemical Company (St. Louis, MO) unless otherwise noted.

2.2. Tissues

Human placentas were obtained from elective pregnancy terminations between 6 and 13 weeks of gestation in accordance with a protocol approved by the Human Subjects Committee of the University of Kansas Medical Center. Samples were taken from placentas at the indicated gestations. Random sampling sites were selected among floating villi and no specific pathologic abnormalities were detected in these curettage specimens upon microscopic examination of the samples.