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Congenital cytomegalovirus infection undermines early development and functions of the human placenta

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ABSTRACT

Congenital human cytomegalovirus (HCMV) infection is a major viral cause of birth defects, including microcephaly, neurological deficits, loss of hearing and vision, and intrauterine growth restriction. Despite its public health significance, there is no approved treatment for congenital infection during pregnancy; existing antivirals have unacceptable toxicities. The mechanisms of HCMV-induced placental injury, reduced capacity for compensatory development and transmission to the fetus are poorly understood, limiting the development of alternative strategies for clinical management of the disease. Recently, self-renewing, multipotent trophoblast progenitor cells (TBPCs) were reported to reside in the chorion of the human placenta and differentiate into the mature trophoblast subtypes – transport syncytiotrophoblasts and invasive cytotrophoblasts – forming chorionic villi, the functional units of the placenta. HCMV infects TBPCs, reducing the population of progenitor cells and their functional capacity to self-renew, migrate and differentiate. Human TBPCs and chorionic villus explants from first trimester represent relevant models for evaluating efficacies of new antiviral agents in protecting and restoring growth of the developing placenta in response to adverse conditions. Correlating pathology from complications of congenital HCMV infection with impaired development in the tissue environment of anchoring villus explants and defects in TBPC differentiation may enable identification of molecular pathways that could serve as targets for intervention. Here we summarize studies that could open up novel avenues of research on potential therapeutics to sustain placental development, promote differentiation and improve function and pregnancy outcomes.

1. Congenital HCMV infection impairs development of the human placenta

Human cytomegalovirus (HCMV) is the most common infectious cause of birth defects in congenitally infected newborns [1,2]. Among live births, more babies are affected by HCMV infection *in utero* than by other, better known conditions, including Down syndrome, fetal alcohol syndrome and neural tube defects [3,4]. Each year in the United States about 40,000 infants are born with congenital HCMV, 400 will succumb in childhood and 8000 will have permanent disabilities [5]. Virus transmission occurs throughout pregnancy, but disease is more severe when primary maternal infection occurs in the first trimester of gestation [6–9]. Symptomatic infants can have microcephaly, neurological defects, sensorineuronal deafness, retinopathy and intrauterine growth restriction (IUGR) [2]. Infection in the third trimester is often asymptomatic but can lead to progressive hearing loss [10,11].

Although fetal infection likely underlies the long-term neurological defects caused by congenital infection, negative outcomes can result from infection of the placenta alone, without evidence of transmission [12]. Maternal immunity and placental factors that determine transmission to the fetus and the risk of negative outcomes are still not understood. Infected placentas show pathological changes that undermine transport functions during late pregnancy, including fibrinoids, avascular villi, calcification, edema and inflammation with leukocytic infiltration. Some or all of these may be present in cases of symptomatic disease [13–15], stillbirth [16] and IUGR with underlying congenital infection [17]. Diagnosis of virus transmission and fetal infection entails amniocentesis and detection of HCMV DNA in amniotic fluid beginning at mid-gestation. However, high viral load fails to correlate with poor outcome [18], implying that disease severity is not tightly linked to

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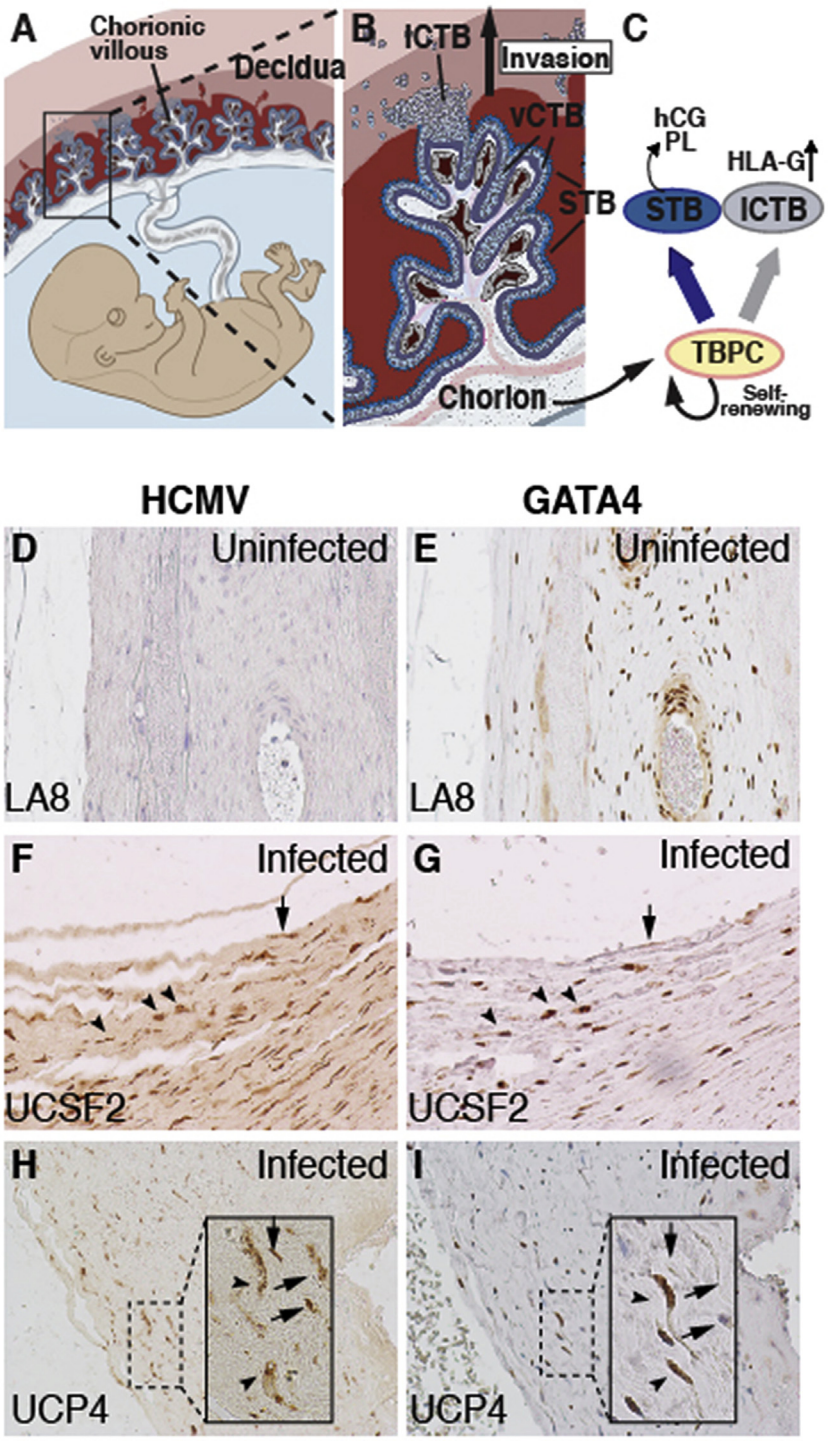

Fig. 1. Anatomy of the human placenta. (A, B) Chorionic villi, the functional units of the placenta, consist of syncytiotrophoblasts (STBs), the outermost cell layer in contact with maternal blood (dark red), villous cytotrophoblasts (vCTBs) immediately below the STB, and invasive CTBs (iCTBs) that remodel the uterine decidua. Both STBs and iCTBs differentiate from vCTBs that are derived from self-renewing TBPCs (B, C) [23,57]. STBs secrete hCG, human chorionic gonadotropin, and PL, placental lactogen. iCTBs express HLA-G (C). HCMV proteins detected in cells of chorionic membranes in placentas from congenital infection. Immunohistochemical staining for HCMV proteins (D, F and H) and GATA4 (E, G and I) in adjacent sections of an uninfected placenta (D and E; LA8 [17,23]), and two placentas from cases of symptomatic congenital infection (F-I; UCSF2 from delivery at UCSF and UCP4 from UCSF Pathology standing collection [23]). HCMV protein-positive cells (F and H) had a lower intensity of GATA4 expression, which marked TBPC progenitor cells (G and I) in the chorion (arrow). Some HCMV protein-positive cells still express GATA4 (arrowhead).

virus production. Amniotic fluid from congenital infection contains elevated levels of inflammatory cytokines and chemokines [19] potentially contributing to fetal pathology and risk of pregnancy complications. A subset of first-trimester placentas from uncomplicated pregnancies [20–22] and placentas at term from pregnancies not initially diagnosed for primary maternal HCMV infection by serological methods contained HCMV proteins, suggesting that underlying congenital infection contributes more

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