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Review article

Interleukin 11 is upregulated in preeclampsia and leads to inflammation and preeclampsia features in mice

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ABSTRACT

Preeclampsia is a dangerous pregnancy complication, which is often associated with fetal growth restriction and can have serious life-long effects for both mother and baby. While the establishment of the placenta in the first trimester is the sentinel event in the development of preeclampsia little is known of the critical mechanisms of placentation that lead to the syndrome. Locally produced inflammatory cytokines are thought to play a role in the development of preeclampsia. This review summarizes the evidence that interleukin 11 is dysregulated in preeclampsia and contributes to the initiation of preeclampsia via effects on placentation. It discusses the benefits and drawbacks of targeting IL11 as a novel treatment option for preeclampsia.

1. Introduction

Preeclampsia is a pregnancy-induced disorder characterised by hypertension and proteinuria, unique to humans, affecting ~8% of pregnancies (Sibai et al., 2005). The only cure for the disease is removal of the placenta. The etiology is poorly understood (Kaufmann et al., 2003), nevertheless, there is substantial evidence showing abnormal placentation is crucial to the underlying cause. During placentation, highly invasive extravillous trophoblasts (EVT) acquire vascular-like properties to remodel maternal uterine spiral arterioles, which is complete in the first trimester. This creates low-resistance, large-diameter vessels to promote utero-placental blood supply and sustain fetal growth and development (Brosens et al., 1972; Pijnenborg, 1994). It is widely accepted that inadequate trophoblast invasion and impaired uterine spiral artery remodeling are initiating factors in the development of preeclampsia (Naicker et al., 2003), however little is known of the mechanisms of placentation. Interleukin (IL)11 is an IL6 family cytokine with well-established functional roles in the cycling endometrium and early initiation of pregnancy during embryo implantation and endometrial stromal cell decidualization (Bilinski et al., 1998; Robb et al., 1998; Dimitriadis et al., 2000, 2002; White et al., 2007). IL11 mediates human trophoblast migration and invasion in vitro (Paiva et al., 2007, 2009b). Recently IL11 has been demonstrated to contribute to the regulation of placentation and lead to the development of features of preeclampsia, including hypertension and proteinuria in mice (Paiva et al., 2007, 2009b; Winship et al., 2015). The purpose of this review is to evaluate the evidence that IL11 contributes to the initiation of preeclampsia and mediates a maternal inflammatory response and to critically analyze the benefits and drawbacks of targeting IL11 as a novel treatment option for preeclampsia.

2. Placental development and preeclampsia

Tightly regulated trophoblast cell proliferation, differentiation, migration and invasion ensure normal placental development and healthy pregnancy (Burton et al., 2010). Conversely, abnormal trophoblast function is associated with adverse pregnancy outcomes, such as the pregnancy disorders preeclampsia and intrauterine growth restriction (IUGR) (Redman and Sargent, 2005).

During placentation, cytotrophoblasts derived from the embryonic trophectoderm proliferate and differentiate into syncytiotrophoblast and highly invasive extravillous trophoblast (EVT) (Red-Horse et al., 2004). EVTs migrate into the maternal decidua and myometrium to penetrate the lumen of the spiral arterioles, replacing endothelial cells in a remodeling the uterine spiral arteries. This creates low-resistance, large-diameter vessels that facilitate the increased blood supply to the placenta which is required to sustain fetal growth and development (Burton et al., 2010).

It is widely accepted that inadequate trophoblast invasion and spiral artery remodeling is a key event in the etiology of the pregnancy disorders preeclampsia and intrauterine growth restriction (IUGR) (Redman and Sargent, 2005). This can lead to reduced utero-placental

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arterial flow and ischemia due to irregular placental perfusion causing damage to the placenta. Placental oxidative stress can ensue and result in the generation of reactive oxygen species, pro-inflammatory cytokines and altered production of angiogenic regulators, all characteristics of a preeclamptic placenta (Burton et al., 2009). This increased placental secretion of pro-inflammatory cytokines (Otun et al., 2011) and angiogenic regulators, such as soluble fms-like tyrosine kinase 1 (s-Flt1) (Maynard et al., 2003) are thought to contribute to widespread maternal endothelial dysfunction. The administration of human pre-eclamptic patient sera to mice induces preeclampsia feature in vivo (Kalkunte et al., 2010), advocating that it is circulating factors, which likely contribute to the pathogenesis of endothelial dysfunction. Pre-eclampsia is diagnosed by hypertension and proteinuria, while clinical symptoms can include peripheral and/or cerebral edema. Symptoms can differentially manifest during the second (early-onset, EO), or third (late-onset, LO) trimester (Vatten and Skjaerven, 2004). In addition to maternal symptoms, preeclampsia may be associated with prematurity and intrauterine growth restriction (IUGR) (Sibai et al., 2005; Gruslin and Lemyre, 2011). Together these disorders affect approximately 8% of all pregnancies and contribute to impaired maternal and fetal health (Sibai et al., 2005). Despite much research over the past few decades, there are no early detection tests and a complete lack of pharmacological treatment options for these disorders (Kaufmann et al., 2003).

Adverse placental development is central to the development of preeclampsia, the regulation of EVT function and their interactions with the decidua have been the source of much investigation. While placentation is poorly understood, there is strong evidence that locally produced factors and particularly, pro-inflammatory cytokine signalling plays a major role in this process (Dimitriadis et al., 2005; Salamonsen et al., 2009).

3. Interleukin-11 signalling in the female reproductive tract

IL11 is a pleiotropic cytokine that regulates cell cycle, invasion and migration in numerous cell types (Paul et al., 1990; Paiva et al., 2009a; Putoczki and Ernst, 2010; Winship et al., 2016a); all functions critical to placental development. IL11 is a member of the IL6 family of cytokines, which also includes leukemia inhibitory factor (LIF), oncostatin M, cardiotrophin-1, ciliary neurotrophic factor, cardiotropin-like cytokine/cytokine-like factor, IL27 and IL31. With the exception of IL31, this family shares a common accessory signalling molecule, glycoprotein (gp) 130, though IL11 signals via its' own distinct ligand-specific receptor (R) α subunit, inferring non-redundancy with other family members (Yamasaki et al., 1988; Hilton et al., 1994; Heinrich et al., 2003).

Upon IL11 ligand binding, the IL11Rα chain dimerizes with gp130 and forms a hexameric complex (Matadeen et al., 2007). This triggers phosphorylation of the signal transducer and activator of transcription (STAT) family of transcription factors (Heinrich et al., 2003) which translocate to the nucleus to activate target genes (Heinrich et al., 2003). IL11 is capable of activating numerous additional signalling pathways, including the mitogen activated protein kinase/extracellular signal-regulated kinase (MAPK)/(ERK), the Src-family kinases (Fuhrer and Yang, 1996), or the phsophotidylinositol-3 kinase (PI-3K) pathways (Heinrich et al., 2003). The relative importance of each signaling pathway is tissue specific (Du and Williams, 1994).

Our findings and others consistently demonstrate that IL11 signals via the JAK/STAT3 pathway in female reproductive tissues, including the human endometrium (Dimitriadis et al., 2006b) and primary human EVT (Corvinus et al., 2003; Bao et al., 2006; Paiva et al., 2007, 2009b). In the same manner, IL11 signalling via STAT3 may also upregulate trophoblast-derived factors that inhibit their invasiveness. Accordingly, we and others have shown that IL11 impedes trophoblast cell invasion in vitro (Paiva et al., 2009b; Suman et al., 2012). More recent findings confirmed IL11 likely acts via STAT3 in the placenta and decidua in mice (Winship et al., 2015). In this study exogenous IL11 activated STAT3, but not ERK in the mouse placenta and decidua. Furthermore, IL11 withdrawal alleviated IL11-induced STAT3 activation, supporting that IL11 likely regulates placentation in vivo at least in part via STAT3. To confirm this however, use of STAT3 inhibitor in vivo in mice could be performed (Figs. 1 and 2).

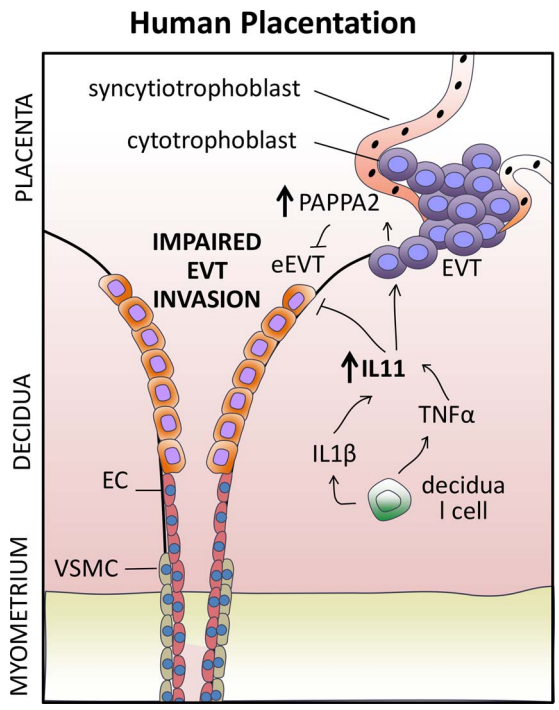

Fig. 1. Actions of Interleukin 11 (IL11) during first trimester human placental development. In humans, the pro-inflammatory cytokines IL1β and TNF-α stimulate IL11 in the decidua. IL11 acts to inhibit invasion of the extravillous trophoblast (EVT) into the endometrium, impairing endovascular (e)EVT remodeling of maternal spiral arterioles, and this occurs partly via up-regulation of PAPPA2. Elevated serum IL11 protein is detected in women that develop EO PE and this is likely secreted from the placental syncytium. EC endothelial cell; VSMC vascular smooth muscle cell.

4. Expression of the IL11 and its signalling complex in the female reproductive tract in humans and mice

In the human endometrium, levels of IL11 protein peak during the mid-secretory phase when the endometrium is receptive to an implanting blastocyst (Dimitriadis et al., 2000). The pattern of expression of IL11 and its signalling receptor, IL11Rα in the endometrium have previously been reviewed (Winship et al., 2016a), suggesting that IL11 signalling contributes to receptivity and decidualization. IL11 promotes primary human endometrial stromal cell decidualisation in vitro (Dimitriadis et al., 2002). IL11 levels are abnormally low in endometrium of infertile women with endometriosis and women with unexplained infertility (Dimitriadis et al., 2006a, 2007). In women, absent or low decidual and villous trophoblast IL11 expression is associated with spontaneous abortion and anembryonic pregnancy (Koumantaki et al., 2001; Chen et al., 2002).

In the placenta, IL11 and IL11Rα protein are produced by placental chorionic villous syncytiotrophoblast and cytotrophoblast cells, as well as endovascular EVT and decidual cells during the first trimester (Paiva et al., 2007) and by contrast in the second and third trimester, are produced at lower levels (Winship et al., 2015).

In mice, uterine IL11 synthesis peaks during decidualization (Bilinski et al., 1998; Robb et al., 1998). Both IL11 and IL11Rα localize to placental and endovascular trophoblast and endothelial cells in mouse implantation sites throughout gestation (Winship et al., 2015), reflecting the localisation patterns of women.