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Review

Vessel remodelling, pregnancy hormones and extravillous trophoblast function

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ABSTRACT

During early human pregnancy, extravillous trophoblast (EVT) cells from the placenta invade the uterine decidual spiral arterioles and mediate the remodelling of these vessels such that a low pressure, high blood flow can be supplied to the placenta. This is essential to facilitate normal growth and development of the foetus. Defects in remodelling can manifest as the serious pregnancy complication pre-eclampsia. During the period of vessel remodelling three key pregnancy-associated hormones, human chorionic gonadotrophin (hCG), progesterone (P_4) and oestradiol (E_2), are found in high concentrations at the maternal–foetal interface. Potentially these hormones may control EVT movement and thus act as regulators of vessel remodelling. This review will discuss what is known about how these hormones affect EVT proliferation, migration and invasion during vascular remodelling and the potential relationship between hCG, P_4, E_2 and the development of pre-eclampsia.

Contents

1. Extravillous trophoblast

A successful human pregnancy requires significant invasion of maternal uterine decidual tissue by trophoblast cells to facilitate access of the developing placenta and foetus to the maternal blood supply. Failure to achieve this can result in clinically important pregnancy complications such as pre-term delivery, pre-eclampsia (PE), and foetal growth restriction. The invasive extravillous trophoblast (EVT) arises from a subpopulation of cytotrophoblast located at the tips of the placental anchoring villi which undergo an epithelial–mesenchymal transition. The EVT migrates away from the villi and invades deeper through the endometrium and the inner third of the myometrium, specifically targeting the associated segments of the uterine decidual spiral arterioles. EVT invasion takes two major routes; endovascular through the lumens of

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Table 1
Changes in hCG, P_4, E_2 and decidual spiral arterioles through gestation Summary of changes in decidual spiral arterioles and the concentrations of hCG, P_4 and E_2 throughout human pregnancy. Values are intended as a guide only, sourced as indicated. hCG [mIU/mL × 10^3], P_4 [nmol/L], E_2 [nmol/L]. Conversion factors: P_4 ng/mL to nmol/L, ×3.18; E_2 ng/mL to nmol/L, ×3.68. TC, trophoblast cells; EC, endothelial cells; VSMC, vascular smooth muscle cells. Arrows indicate no further change, shading indicates the change in concentrations; lighter shading = lowest concentrations, darker shading = highest concentrations.

Weeks	0	4	8	12	16	20	24	28	32	36	40
hCG[a]	0	0.24	95.3	95.7	32.3	21.3	→				
P_4	1.4-12.1[b]	58.2[c]	56.6[c]	113[c]	116[c]	204[d]	247[d]	273[d]	224[e]	495[d]	584[f]
E_2	0.34-0.45[b]	2.6[c]	4.1[c]	7.0[c]	11[c]	30.8[d]	34[d]	34[d]	22.7[e]	52[d]	53.4[f]
Vessel changes[g-i]	Unmodified vessels	Vessel priming	TC invasion Loss of EC and VSMC	TC plugs dissolve	TC infiltration ceases	Remodelling complete	→				

[a] Cole (2009).
[b] Rutanen et al. (1984).
[c] Hassiakos et al. (1991).
[d] Tulchinsky et al. (1972).
[e] Soldin et al. (2005).
[f] O'Leary et al. (1991).
[g] Burton et al. (1999).
[h] Kaufmann et al. (2003).
[i] Pijnenborg et al. (2006).

spiral arterioles or interstitial through the maternal tissue (Pijnenborg et al., 2006). Veins remain relatively un-invaded but the factors responsible for this arterial–venous discrimination are not well understood (Pijnenborg et al., 2006).

1.1. Functional significance of EVT invasion: vascular remodelling

EVT invasion of uterine spiral arterioles brings about functional and structural changes essential for ensuring that the vessels can deliver low pressure, high blood flow without hindrance, especially important in later pregnancy when the foetus exhibits exponential growth. Remodelling is completed by the mid-second trimester and occurs in three stages (Pijnenborg et al., 2006). The essential first step is trophoblast-independent, decidual-associated remodelling during which the decidualised endometrium is thought to control trophoblast movement via the expression of regulators such as matrix metalloproteinases (MMPs), endocrine factors and cytokines (Burton et al., 2009; Pijnenborg et al., 2006). In the latter two stages, EVT that has invaded and is positioned in or around the spiral arterioles is thought to induce apoptosis of, and replace, both the vascular smooth muscle and endothelial cells (Ashton et al., 2005; Keogh et al., 2007; Whitley and Cartwright, 2009). Consequently, the spiral arterioles become dilated, low in resistance, deprived of sympathetic innervations and unresponsive to vasoconstrictive factors (Burton et al., 2009; Chang and Lubo, 2008). Such changes, together with angiogenesis, allow a 40-fold increase in uterine blood flow to the placenta (Chang and Lubo, 2008).

1.2. Roles of matrix metalloproteinases in the invasion process

EVT invasion is aided by the secretion of MMPs, especially members of the gelatinase family including MMP-2 and MMP-9 (Cohen et al., 2006; Isaka et al., 2003; Staun-Ram et al., 2004). The measurement of MMP-2 and MMP-9 activities are indicators of the invasive capability of trophoblast and they are expressed at high concentrations by trophoblast in early but not late gestation (Cohen et al., 2006; Staun-Ram et al., 2004; Xu et al., 2000). Functional inhibition of MMP-9 (Bischof et al., 1995; Librach et al., 1991) and MMP-2 (Isaka et al., 2003) have been shown to greatly reduce or even completely abolish the invasive capability of trophoblast *in vitro* (Isaka et al., 2003; Librach et al., 1991). Such effects are not seen with the inhibition of other classes of enzymes that also play a role in trophoblast invasion (Librach et al., 1991). Recent work has demonstrated a role for another member of the MMP family, MMP-12, in EVT-mediated elastin breakdown during spiral arteriole remodelling (Harris et al., 2010).

2. Endocrine regulation of trophoblast functions

A multitude of factors including endocrine regulators, oxygen concentration, immune cells, and haemodynamics contribute to the regulation of EVT functions. This review will explore the role of three pregnancy-associated hormones present at high concentrations at the foetal–maternal-interface in regulating EVT functions and vascular remodelling: human chorionic gonadotropin (hCG), progesterone (P_4), and oestradiol (E_2). hCG produced by trophoblast is mostly secreted into maternal blood and thus its placental tissue concentration is relatively low. Serum concentrations of hCG peak at around the 8–12th week of gestation before gradually decreasing over the second and third trimesters until term (Cole, 2009; Edelstam et al., 2007; Table 1). P_4 and E_2 concentrations rise throughout pregnancy, peaking at the end of gestation. P_4 undergoes an initial rise then plateaus, even falling in some instances, at around the 7–9th week during the period of the luteo-placental shift before rising steadily again from about the 20th week of gestation (Distler et al., 1978; Edelstam et al., 2007; Mishell et al., 1973; Table 1). E_2 concentrations rise steadily throughout pregnancy (Distler et al., 1978; Edelstam et al., 2007; Mishell et al., 1973; Table 1). P_4 and E_2 potentially exist in placental tissue at concentrations that are considerably higher than that in maternal blood (King and Critchley, 2010). As EVT predominantly takes an interstitial rather than endovascular route of invasion (Pijnenborg et al., 2006), placental tissue concentrations of hormones