REVIEW

# Maternal growth factor regulation of human placental development and fetal growth

**Karen Forbes** and **Melissa Westwood**

School of Biomedicine, Maternal and Fetal Health Research Centre, Manchester Academic Health Sciences Centre, University of Manchester, Manchester M13 9WL, UK

(Correspondence should be addressed to M Westwood; Email: melissa.westwood@manchester.ac.uk)

## Abstract

Normal development and function of the placenta is critical to achieving a successful pregnancy, as normal fetal growth depends directly on the transfer of nutrients from mother to fetus via this organ. Recently, it has become apparent from both animal and human studies that growth factors within the maternal circulation, for example the IGFs, are important regulators of placental development and function. Although these factors act via distinct receptors to exert their effects, the downstream molecules activated upon ligand/receptor interaction are common to many growth factors. The expression of numerous signaling molecules is altered in the placentas from pregnancies affected by the fetal growth complications, fetal growth restriction, and macrosomia. Thus, targeting these molecules may lead to more effective treatments for complications of pregnancy associated with altered placental development. Here, we review the maternal growth factors required for placental development and discuss their mechanism of action.

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## Introduction

Aberrant fetal growth affects as many as 7% of babies – ~50 000 infants born each year in the UK (Population, Censuses & Surveys Office 2007). Many infants born with inadequate growth (fetal growth restriction; FGR) die, and others require costly neonatal intensive care, while excessive fetal growth (macrosomia) is associated with increased intrapartum risks to the mother and child. In addition, these conditions have a life-long impact on health including elevated childhood morbidity and mortality and an increased risk of developing cardiovascular disease and diabetes in adulthood (Barker 2006). Currently, there are no treatments for cases of altered fetal growth. It is well established that many fetal growth disorders are rooted in defective placental development, thus in order to make significant progress in this area, a better understanding of the mechanisms regulating placental growth is needed.

## Placental development and fetal growth

In chorionic villi of the human placenta (Fig. 1), cytotrophoblasts are a progenitor stem cell population which continuously proliferate and differentiate into one of two subtypes; extravillous trophoblasts that migrate into the maternal decidualized endometrium and remodel the spiral arteries to optimize the supply of oxygen and nutrients to the placenta and fetus; or syncytiotrophoblast, a multinucleated epithelia which acts both to protect the fetus from the maternal immune response and as a nutrient and gas exchange membrane (Fig. 1; Kingdom *et al.* 2000). As the growth and thus nutrient demands of the fetus increase with pregnancy progression, the syncytial surface area must also increase to ensure sufficient transfer of nutrients to the fetus. The villous syncytiotrophoblast layer has a short lifespan with terminally differentiated and apoptotic elements shedding continuously into maternal circulation. A process to renew and expand the syncytial layer throughout pregnancy is therefore required. The syncytiotrophoblast layer has no transcriptional activity, and hence during pregnancy, it is maintained by the continual proliferation, differentiation, and fusion of cytotrophoblasts.

Consequently, cytotrophoblast proliferation is important for placental growth, especially during the first trimester, when the tissue grows rapidly. Increased or decreased rates of trophoblast turnover have been associated with different tissue pathologies and are linked to enhanced (macrosomic) or reduced (FGR) fetal growth (Jansson & Powell 2006). In these conditions, the surface area available for transfer of


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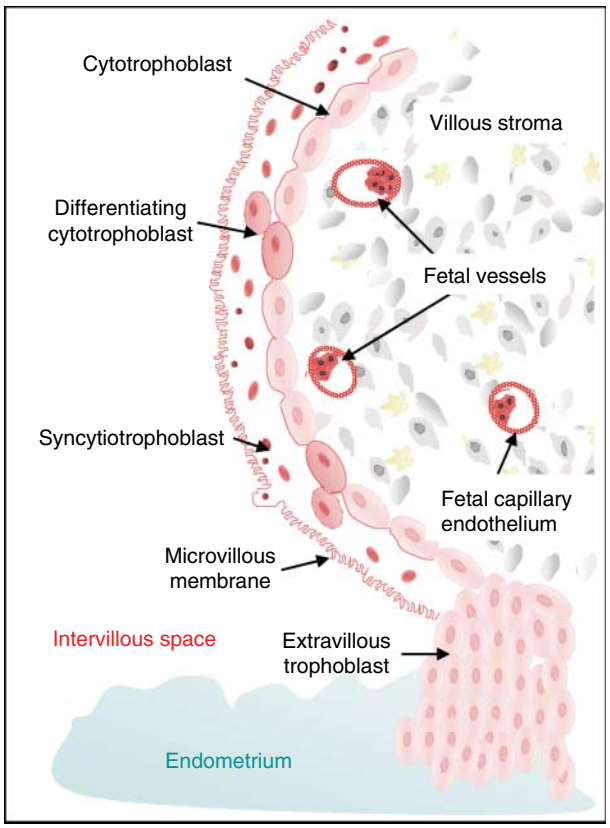


**Figure 1** Schematic diagram of the first trimester human placenta. Cytotrophoblasts proliferate and differentiate into one of two subtypes, the invasive extravillous trophoblasts or the terminally differentiated non-proliferative syncytiotrophoblast. The syncytiotrophoblast functions as a protective barrier for the fetus and is the epithelial surface where exchange of nutrients and gases between the maternal and fetal circulations occurs. The villous stroma lies directly below the cytotrophoblast layer and contains numerous different cell types including placental macrophages (Hofbauer cells), fibroblasts, and endothelial cells.

nutrients is altered: an increase in trophoblast proliferation results in enhanced placental nutrient transfer in macrosomia, while the converse occurs in FGR (Jansson & Powell 2006). Since extravillous trophoblasts invade the maternal circulation and are required to establish an oxygen supply to the fetus, it is unsurprising that alterations in this aspect of trophoblast function are also associated with pregnancy complications such as FGR and pre-eclampsia (Kaufmann *et al.* 2003); establishing the mechanisms of trophoblast invasion and spiral artery remodeling is the current focus of many research groups (Goldman-Wohl & Yagel 2002, Lyall 2006, Pijnenborg *et al.* 2006, Knofler *et al.* 2008, Harris *et al.* 2009).

Recently, several studies have suggested that soluble factors in the maternal circulation, including growth factors, can influence placental development and function (Baczyk *et al.* 2005, Johnstone *et al.* 2005*b*, Sferruzzi-Perri *et al.* 2006, 2007, Moll *et al.* 2007, Forbes *et al.* 2008, 2010*a*,*b*,*c*, Hoffmann *et al.* 2009).

This review will examine the role of such growth factors in the regulation of trophoblast function by briefly discussing their effect on extravillous trophoblast invasion (see the recent review by Knofler (2010) for more detail on this topic), and focussing in detail on the control of villous cytotrophoblast proliferation and function.

## Influence of maternal growth factors on fetal growth

During pregnancy, the levels of growth factors, such as the insulin-like growth factors 1 and 2 (IGF1 and IGF2), epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGF)-2 and FGF4, and members of the transforming growth factor (TGF)-β superfamily, are increased within the maternal circulation, and these elevated levels are sustained throughout gestation, suggesting that they have important roles in promoting the growth of the developing fetus. The levels of some growth factors such as IGFs and EGF correlate with fetal growth, while others such as TGFβ1 are not altered (Table 1). However, all of these growth factors exert their effects via intracellular cascades that utilize common signaling molecules; many of which are dysregulated in fetal growth disorders. Therefore, enhancing the growth factor levels alone may not be sufficient to rescue the placental phenotype; instead, it is likely that greater therapeutic benefits may be achieved by targeting growth factor receptors, or indeed the downstream signaling molecules that are responsible for exerting their mitogenic effects. Here, we discuss each of these growth factors and its signaling cascades in the context of their potential role in regulating placental and fetal growth.

## The IGF axis

IGF1 and IGF2 are two small, highly homologous single-chain polypeptides (Le Roith *et al.* 2001). Although IGF2 can bind to the type-2 IGF/mannose-6-phosphate receptor (IGF2R/M6PR) or the insulin receptor, the classical actions of both IGF1 and 2 are mediated by binding to the type-1 IGF receptor, IGF1R. Ligand access to the receptors is regulated by a family of binding proteins termed IGF-binding proteins (IGFBPs)-1–6. Unsurprisingly, IGFBP levels, particularly IGFBP-1 and IGFBP-3 that are abundant at the maternal–fetal interface, are also correlated with fetal growth (Forbes & Westwood 2008). Although tissue-specific differences exist, all components of the IGF axis have been shown to mediate growth, differentiation, survival, and metabolism in almost every organ of the body (Jones & Clemmons 1995), and numerous animal and human studies have highlighted the importance of their actions for fetal growth and development (Tables 1–3).

The involvement of IGFs in regulating fetal growth was first reported in clinical studies demonstrating that birth

**Table 1** Maternal growth factor concentrations in normal pregnancy and in pregnancies associated with fetal growth disorders

| | **Mother** | | | **Fetus** | | | |
|---|---|---|---|---|---|---|---|
| | Level (ng/ml) in circulation during normal and complicated pregnancy | | | Level (ng/ml) in cord blood during normal and complicated pregnancy | | | Pregnancy pathology associated with ligand or receptor gene defect (refs) |
| | Normal (refs) | FGR (refs) | Macrosomia (refs) | Normal (refs) | FGR (refs) | Macrosomia (refs) | |
| **Growth factor** | | | | | | | |
| EGF | T1 0·1–2·5[1, 2] | ↔[1] | | | | | |
| | T2 0·1–2·5[1, 2] | ↔[1] | | | | | |
| | T3 0·02–2·5[1–3] | ↔[1] | ↑[3] | 3·2[18] | ↓[18] | NR | NR |
| FGF2 | T2 0·04–6[4, 19] | | | 2[19] | | | NR |
| | T3 0·02–6[3–6, 19] | ↔[6] | ↑[3, 5] | 12[5, 19] | ↔[6] | ↑[5] | |
| IGF1 | T1 110–250[1, 7–9] | ↓[1] ↔[7] | | | | | |
| | T2 80–400[1, 7, 10] | ↓[1, 15] ↑[7] | ↔[15] | 20–35[20, 21] | | | Ligand – FGR[27, 28] |
| | T3 110–450[1, 3, 7–14] | ↓[1, 11–13] ↔[7] | ↔[14] ↑[3] | 40–95[14, 20–26] | ↓[23, 26] | ↑[14, 23, 24] | Receptor – FGR[29–31] |
| PDGF | T3 2–600[3, 4, 16] | NR | ↑[3] | NR | NR | NR | NR |
| TGFβ1 | T1 0·35[1] | ↔[1] | | | | | |
| | T2 0·35[1] | ↔[1] | | | | | NR |
| | T3 0·04–0·35[1, 17] | ↔[1] | NR | 5–40[32, 33] | ↓[33] | ↔[33] | |

T, trimester; ↑, increased versus normal pregnancy; ↓, decreased versus normal pregnancy; ↔, no change in normal pregnancy; FGR, fetal growth restriction; NR, not reported. 1 – Hernandez-Valencia *et al.* (2001); 2 – Vuorela *et al.* (2002); 3 – Grissa *et al.* (2010); 4 – Chow *et al.* (2008); 5 – Hill *et al.* (1995); 6 – Wallner *et al.* (2007); 7 – Bhatia *et al.* (2002); 8 – Olausson *et al.* (2010); 9 – Wilson *et al.* (1982); 10 – Hubinette *et al.* (2003); 11 – Holmes *et al.* (1997); 12 – Larsen *et al.* (1996); 13 – Malamitsi-Puchner *et al.* (2007); 14 – Wiznitzer *et al.* (1998); 15 – McIntyre *et al.* (2000); 16 – Morita *et al.* (2001); 17 – Huber *et al.* (2002); 18 – Shigeta *et al.* (1992); 19 – Hill *et al.* (1995); 20 – Langford *et al.* (1998); 21 – Gohlke *et al.* (2004); 22 – Reece *et al.* (1994); 23 – Giudice *et al.* (1995); 24 – Roth *et al.* (1996); 25 – Ong *et al.* (2000); 26 – Verkauskiene *et al.* (2007); 27 – Woods & Savage (1996); 28 – Netchine *et al.* (2009); 29 – Kiess *et al.* (2005); 30 – Walenkamp *et al.* (2006); 31 – Wallborn *et al.* (2010); 32 – Power *et al.* (2002); 33 – Ostlund *et al.* (2002).

weight is positively correlated with cord blood IGF1 levels (Osorio *et al.* 1996, Klauwer *et al.* 1997), and so levels are low in small-for-gestational-age (SGA) infants and are enhanced in large-for-gestational-age babies (Table 1). Evidence for the importance of IGF2 in this regard comes from the observation that the *IGF2* gene is maternally imprinted (Giannoukakis *et al.* 1993). Relaxation of imprinting leads to Beckwith–Wiedemann syndrome in which excess IGF2 is associated with fetal overgrowth (Morison *et al.* 1996, Ward 1997). Subsequent studies using transgenic mice confirmed these clinical observations by demonstrating that mutation of the gene encoding either IGF1 or IGF2 results in offspring that are ∼40% smaller than their wild-type littermates (Efstratiadis 1998; Table 2). More recently, clinical studies have revealed that levels of IGFs within the maternal circulation are also correlated with fetal growth (Table 1) highlighting the potential for maternal IGFs to have an influence on pregnancy outcome (Holmes *et al.* 1997, Hernandez-Valencia *et al.* 2001, Grissa *et al.* 2010).

The mitogenic effects of both IGF1 and 2 are thought to be regulated by IGF1R. Activation of the IGF1R results in autophosphorylation of tyrosine residues in the intracellular β-subunits and subsequent activation of downstream signaling pathways (Jones & Clemmons 1995). The significance of IGF1R in mediating IGF effects on fetal growth was first realized by the study demonstrating that *igf1r* null mice have a more severe phenotype than either the IGF1 or 2 knockout animals as the birth weight of IGF1R knockout mice is reduced by ∼60% when compared to normal littermates (Efstratiadis 1998; Table 3). More recently, the consequence of IGFR abnormalities in human fetal development has been documented. Severe FGR was reported in two infants with a heterozygous missense mutation in the IGF1R gene (Walenkamp *et al.* 2006), and heterozygous mutations within the IGF1R kinase domain (Kruis *et al.* 2010) or extracellular second fibronectin III domain (Wallborn *et al.* 2010) have been reported in two children. Although these individuals had high circulating levels of IGFs, they were both born SGA which was attributed to IGF resistance arising from reduced IGF1R tyrosine phosphorylation or altered cell surface expression respectively.

The type-2 IGF receptor (IGF2R) does not contain tyrosine kinase activity or an autophosphorylation site, and therefore, classically it was suggested that the primary function of this receptor is to clear IGF2 from the circulation; this is supported by the studies demonstrating that mice lacking the IGF2R/M6PR have raised circulating IGF2 levels and much greater birth weights than their wild-type littermates (Lau *et al.* 1994, Efstratiadis 1998), and further highlighting the importance of IGF2 in regulating fetal growth (Table 3).

**Table 2** Contribution of growth factors to fetal weight. The effect of alteration in maternal or fetal (gene knockout) growth factor levels on fetal weight

| | **Mother** | | **Fetus** |
|---|---|---|---|
| | Effect of altered GF levels during pregnancy on fetal weight | | Effect of *GF* gene knockout (refs) |
| | ↑ Maternal levels (refs) | ↓ Maternal levels (refs) | |
| **Growth factor** | | | |
| EGF | Rabbit: 20% ↑[1]<br>Rat: ↔[2]<br>Sheep: ↔[3] | Mouse: 15% ↓[11] | No overt phenotype[12] |
| FGF2 | NR | NR | Neuronal defects; delayed wound healing[13] |
| IGF1 | Guinea-pig: 6–17% ↑[4–6]<br>Mouse: ↑[7]<br>Rat: ↑[7]/↔[8, 9]<br>Sheep: ↔[10] | NR | Growth deficiency – pups 60% of normal birth weight[14] |
| PDGF | NR | NR | Renal, cardiovascular, and hematological abnormalities[15] |
| TGFβ1 | NR | NR | Variable phenotype (background dependent): Embryonic lethal (defective vasculogenesis)[16]/ defective HPG axis[17] |

HPG, hypothalamus–pituitary–gonadal axis; ↑, increased versus normal pregnancy; ↓, decreased versus normal pregnancy; ↔, no change from normal pregnancy; NR, not reported. 1 – Cellini *et al.* (2004); 2 – Ali *et al.* (1990); 3 – Gow *et al.* (1991); 4 – Sferruzzi-Perri *et al.* (2006); 5 – Sferruzzi-Perri *et al.* (2006); 6 – Sohlstrom *et al.* (2001); 7 – Gluckman *et al.*(1992); 8 – Woodall *et al.* (1999); 9 – Gargosky *et al.* (1991); 10 – Bloomfield *et al.* (2002); 11 – Kamei *et al.* (1999); 12 – Luetteke *et al.* (1999); 13 – Ortega *et al.* (1998); 14 – Liu *et al.* (1993); 15 – Leveen *et al.* (1994); 16 – Dickson *et al.* (1995); 17 – Kallapur *et al.* (1999).

IGF affects fetal growth at least in part through its effect on placental development and function. Undoubtedly, endogenous placental production of IGF2 is key since the placentas of mice with placental-specific knockdown of IGF2 have a significantly reduced diffusional exchange surface area, an enhanced barrier thickness, and a reduced permeability for nutrients (Sibley *et al.* 2004, Constancia *et al.* 2005). Placentally derived IGF2 also has a role in promoting trophoblast invasion (Hamilton *et al.* 1998), reportedly by inhibiting molecules such as IGFBP1 and TIMP3 that are produced by the decidua to constrain trophoblast infiltration of maternal tissues (Irwin *et al.* 2001). Similarly, IGF1 from the villous mesenchyme provides a paracrine stimulus for extravillous trophoblast migration (Lacey *et al.* 2002).

However, there is now increasing evidence for the role of maternally derived IGFs in regulating placental development and function (Table 2). In guinea pigs, exogenous supplementation of maternal IGF2 increases the total surface area

**Table 3** Effect of growth factor receptor gene knockout in mice

| | **Phenotype of receptor gene knockout** | **References** |
|---|---|---|
| **Receptor** | | |
| IGF1R | 45% of normal fetal weight | Liu *et al.* (1993) |
| IGF2R | 135% of normal fetal growth | Ludwig *et al.* (1996) |
| EGFR (ErbB1) | At least 40–50% reduction depending on strain | Sibilia & Wagner (1995) and Dackor *et al.* (2009) |
| ErbB2 (HER-2) | Embryonic lethal prior to E11 (neuronal and cardiovascular defects) | Lee *et al.* (1995) |
| ErbB3 | Most mice die between E11.5 and E13.5 (neuronal defects); surviving embryos have 10% reduction in birth weight | Riethmacher *et al.* (1997) |
| ErbB4 | Embryonic lethal between E10 and E11 (neuronal and cardiovascular defects) | Gassmann *et al.* (1995) |
| TGFβRI | Embryonic lethal at E10.5 (abnormal vascular development) | Larsson *et al.* (2001) |
| TGFβRII | Embryonic lethal at E10.5 (abnormal vascular development) | Oshima *et al.* (1996) |
| TGFβRV | Failure of blastocysts to develop into embryos because of implantation failure | Herz *et al.* (1992) |
| FGFR1 | Embryonic lethal (skeletal abnormalities & global proliferation defects) | Muenke & Schell (1995) |
| FGFR2 | Embryonic lethal (skeletal abnormalities global proliferation defects) | Muenke & Schell (1995) |
| FGFR3 | 17–93% of controls (skeletal abnormalities) | Colvin *et al.* (1996) |
| FGFR4 | No phenotype | Weinstein *et al.* (1998) |
| PDGFRα | Embryonic lethal by E16 (neural tube defects) | Soriano (1997) |
| PDGFRβ | Mice die at or shortly before birth (abnormal kidney development and hematological disorders) | Soriano (1994) |

of placenta available for nutrient exchange by 39% (Sferruzzi-Perri *et al*. 2006). Although IGF1 does not affect the surface area of the placenta in guinea pigs, *in vitro* studies in both cultured human primary trophoblast cells and the BeWo choriocarcinoma cell line demonstrate that physiological levels of IGF1 enhance amino acid uptake (Karl 1995, Fang *et al*. 2006). Furthermore, using a first trimester placental explant model which faithfully recapitulates the normal spatial and ontological relationships between the various cells within the placenta, we have recently reported that application of exogenous IGF1 and IGF2 to the syncytial surface (to mimic the maternal circulation) enhances cytotrophoblast proliferation, differentiation, and survival (Forbes *et al*. 2008).

In the human placenta, the IGF1R is localized to all cell types (Table 4) including the trophoblast, villous endothelium, and the mesenchymal core (Fang *et al*. 1997, Holmes *et al*. 1999). Studies of transgenic mice lacking the IGF1R led to the hypothesis that a reduction in the number of placental IGF1R might be a contributing factor in pregnancies complicated by FGR. An immunohistochemical study of placentas from normal and FGR pregnancies found no difference in receptor localization or distribution (Holmes *et al*. 1999); however, it is possible that in these placentas, there may be resistance to IGF caused by alterations in the downstream signaling molecules. Further studies, however, have demonstrated a significant reduction in IGF1R protein levels in FGR (Laviola *et al*. 2005), while elevated placental IGF1R expression has been reported in pregnancies complicated by macrosomia (Jiang *et al*. 2009).

In the placenta, the IGF2R is expressed in the microvillus and plasma membranes of trophoblast (Table 4) but can be proteolytically cleaved, resulting in release of a soluble form of the receptor which, when bound to IGF2, results in degradation of IGF2 and inhibition of its mitogenic actions. Loss of this receptor in mice results in placentomegaly (Wylie *et al*. 2003) and fetal overgrowth (Lau *et al*. 1994), and it has been reported in humans that the molar ratio of IGF2 to soluble IGF2R is significantly related to placental development and birth weights (Ong *et al*. 2000). Until recently, it was thought that the role of IGF2R was to prevent excessive IGF2 effects on the placenta; however, there are now studies to suggest that placental IGF2R is also involved in transducing extracellular signals. Studies in guinea pigs have reported that IGF2R can partially mediate the effects of IGF2 in enhancing placental development and nutrient delivery to promote fetal growth (Sferruzzi-Perri *et al*. 2008), and both IGF2 and human chorionic gonadotropin increase trophoblast migration via the IGF2R (McKinnon *et al*. 2001, Zygmunt *et al*. 2005). The IGF2R does not have any tyrosine kinase activity, thus the mechanism by which the receptor exerts these effects is unclear, although work in other systems has suggested that activation of IGF2R leads to the generation of sphingosine-1-phosphate and consequent signaling through receptors coupled to Gi2 protein (Murayama *et al*. 1990).

## Epidermal growth factor family

EGF, a polypeptide originally isolated from mouse salivary glands (Cohen 1962), first received attention for its ability to stimulate epithelial growth and differentiation when injected into newborn mice (Scott *et al*. 1983). Since then, it has become apparent that EGF has mitogenic roles in most organs within the body (Casalini *et al*. 2004), thus it is unsurprising that EGF also regulates fetal growth and development. In addition to EGF itself, the EGF family comprises 14 different

**Table 4** Localization of growth factor receptors within the human placenta

| Receptor | Localization in human placenta | References |
|---|---|---|
| IGF1R | Microvillus membrane, syncytiotrophoblast, cytotrophoblast, and villous stroma | Fang *et al*. (1997), Holmes *et al*. (1999) and Kita *et al*. (2003) |
| IGF2R | Microvillus membrane and syncytiotrophoblast | Fang *et al*. (1997) |
| EGFR (ErbB1) | Syncytiotrophoblast and cytotrophoblast | Maruo & Mochizuki (1987), Jokhi *et al*. (1994), Tuncer *et al*. (2000), Kita *et al*. (2003) and Tanimura *et al*. (2004) |
| ErbB2 (HER-2) | Extravillous trophoblast | Jokhi *et al*. (1994) and Tanimura *et al*. (2004) |
| ErbB3 | Syncytiotrophoblast, cytotrophoblast, and extravillous trophoblast | Tuncer *et al*. (2000) |
| ErbB4 | Syncytiotrophoblast, cytotrophoblast, and extravillous trophoblast | Tuncer *et al*. (2000) and Tanimura *et al*. (2004) |
| TGFβRI | Microvillus membrane, syncytiotrophoblast, and cytotrophoblast | Xuan *et al*. (2007) and Forbes *et al*. (2010*c*) |
| TGFβRII | Syncytiotrophoblast | Xuan *et al*. (2007) and Forbes *et al*. (2010*c*) |
| TGFβRV | Microvillus membrane | Forbes *et al*. (2010*c*) |
| FGFR1 | Villous stroma | Anteby *et al*. (2005) |
| FGFR2 | Villous stroma and cytotrophoblast | Anteby *et al*. (2005) and Baczyk *et al*. (2005) |
| FGFR3 | Villous stroma | Anteby *et al*. (2005) |
| FGFR4 | Villous stroma and syncytiotrophoblast | Anteby *et al*. (2005) |
| PDGFR | Syncytiotrophoblast and cytotrophoblast | Kita *et al*. (2003) |

ligands (Normanno *et al*. 2006), including heparin-binding EGF, TGF-α, and neuregulin (NRG1). However, the role of these growth factors in fetal growth regulation is unclear.

EGF exerts its effects by binding to its receptor EGFR (also known as the erythroblastic leukemia viral oncogene homolog (ErbB)-1) to stimulate intrinsic tyrosine phosphorylation activity and subsequent activation of pro-mitogenic signaling cascades (Prenzel *et al*. 2001), while the other family members bind with distinct affinities to one of four ErbB receptors (1–4) to influence cellular events (Harris *et al*. 2003). Each of the receptors is expressed in the placenta (Tables 4 and 5); ErbB2–4 are expressed both in villous trophoblast and in extravillous trophoblast (Tuncer *et al*. 2000, Tanimura *et al*. 2004), but EGFR (ErbB1) is expressed only in villous trophoblast. Alterations in EGFR function are associated with reduced placental and embryonic growth both in mice (Dackor *et al*. 2009; Tables 2 and 3) and in humans (Fondacci *et al*. 1994; Tables 1 and 2). Taken together, these studies suggest that signaling via EGFR is important for mediating villous trophoblast function and placental development. This role for EGF/EGFR was confirmed following the discovery that in mice, maternal levels of circulating EGF correlate with fetal growth (Kamei *et al*. 1999), and that EGFR-deficient mice had significantly smaller placentas and displayed severe FGR (Miettinen *et al*. 1995). Further evidence for the importance of EGF in regulating placental development and function comes from *in vitro* studies using human placental cell lines, isolated primary trophoblasts, and explant tissue. EGF increases trophoblast differentiation (Maruo *et al*. 1987, Barnea *et al*. 1990, Garcia-Lloret *et al*. 1996), inhibits trophoblast apoptosis (Johnstone *et al*. 2005*a*,*b*, Moll *et al*. 2007), and promotes trophoblast proliferation (Li & Zhuang 1997). Similar models have been used to demonstrate that EGF also stimulates extravillous trophoblast invasion (LaMarca *et al*. 2008, Han *et al*. 2010), and the work by Bass *et al*. (1994) suggests that the stimulus is most likely maternally derived. More recently, intra-amniotic infusion of EGF was reported to normalize fetal weight in a rabbit model of FGR (Cellini *et al*. 2004) suggesting that targeting the EGF cascade may improve fetal growth.

## Transforming growth factor-β

The TGFβ superfamily contains numerous different ligands including TGFβs, activins, and bone morphogenic proteins (Jones *et al*. 2006). Members of the TGFβ family ligands exert their effects by binding to the type-II TGFβ receptor (TGFβRII) which then dimerizes with the type-I TGFβ receptor (TGFβRI). This dimerization initiates the receptor's serine/threonine kinase activity and induction of divergent signaling cascades that regulate multiple cellular processes including proliferation, migration, and differentiation (Wrighton *et al*. 2009). Studies in mice have demonstrated that knockout of either TGFβRI or TGFβRII results in severe growth restriction, and that the animals die *in utero* (Oshima *et al*. 1996, Larsson *et al*. 2001) suggesting that signaling by these receptors is important for regulating fetal growth (Table 3).

Although TGFβ1 levels are elevated in the maternal circulation during pregnancy (Power *et al*. 2002), its role in regulating fetal growth is unclear. TGFβ1 levels are not correlated with fetal growth (Hernandez-Valencia *et al*. 2001), but a study demonstrating that maternal TGFβ1 can rescue the embryonic lethal phenotype of TGFβ1 knockout mice (Letterio *et al*. 1994) suggests that the growth factor does have an important role during pregnancy (Tables 1 and 2). Indeed, it is well documented that TGFβ1 functions at the maternal–fetal interface to inhibit extravillous trophoblast migration and invasion (Jones *et al*. 2006, Knofler 2010), seemingly by up-regulating integrin and protease inhibitor expression (Irving & Lala 1995, Karmakar & Das 2002); however, its role within the chorionic villous remains controversial.

**Table 5** Localization of growth factor receptors in the murine placenta

| | Localization in murine placenta | References |
|---|---|---|
| **Receptor** | | |
| IGF1R | Not reported | |
| IGF2R | Labyrinth and trophoblast giant cells | Senior *et al*. (1990) |
| EGFR (ErbB1) | Maternal decidua, trophoblast giant cells, and spongiotrophoblast cells | Dackor *et al*. (2007) |
| ErbB2 (HER-2) | Not detectable | Dackor *et al*. (2007) |
| ErbB3 | Maternal decidua and trophoblast giant cells | Dackor *et al*. (2007) |
| ErbB4 | Maternal decidua and trophoblast giant cells | Dackor *et al*. (2007) |
| TGFβRI | Trophoblast giant cells, ectoplacental cone and maternal decidua | Mariano *et al*. (1998) |
| TGFβRII | Trophoblast giant cells, ectoplacental cone and maternal decidua | Mariano *et al*. (1998) |
| TGFβRV | Spongiotrophoblast and maternal decidua | Teesalu *et al*. (1998) |
| FGFR1 | Not reported | |
| FGFR2 | Not reported | |
| FGFR3 | Trophoblast giant cells | Rappolee *et al*. (1998) |
| FGFR4 | Trophectoderm | Rappolee *et al*. (1998) |
| PDGFR | Labyrinth, spongiotrophoblast and trophoblast giant cells | Bidwell *et al*. (1995) |

Studies in both mice and humans have reported that TGFβ1 promotes cytotrophoblast differentiation into syncytiotrophoblast (or labyrinth in mice; Graham *et al.* 1992, Selesniemi *et al.* 2005), while others have suggested that TGFβ1 inhibits this aspect of trophoblast function (Morrish *et al.* 1991, Song *et al.* 1996, Richard *et al.* 2008). Further controversies come from studies to investigate the mitogenic effects of TGFβ within the placenta. In a cell line generated from isolated primary trophoblast, TGFβ inhibits proliferation (Graham *et al.* 1992), but more recently, we have reported that TGFβ1 promotes cytotrophoblast proliferation in first trimester explants (Forbes *et al.* 2010*c*). Although classically TGFβ1 was described as a negative regulator of cellular proliferation by activating the TGFβRI/II Smad2 signaling cascade, our data are consistent with other reports suggesting that the Smad2 and mitogen-activated protein kinase (MAPK) pathways can interact to promote proliferation in the presence of TGFβ (Javelaud & Mauviel 2005, Zhang 2009).

It is likely that the conflicting data reflect differential receptor expression by the various models (Tables 4 and 5), as the level of TGFβ receptor expression within cells and tissues influences the outcome of TGF treatment (Rojas *et al.* 2009). Indeed, we have shown that although each of the TGFβ receptors is expressed in human placenta, the distribution varies, and altering levels of TGFβRII using siRNA resulted in altered responsiveness to maternal factors (Forbes *et al.* 2010*c*). It has yet to be established whether placental TGFβR expression and signaling responsiveness to ligands are altered in FGR and macrosomia, but drugs to target this level of the cascade could potentially prove to be beneficial.

## Fibroblast growth factors

The FGFs are a family comprising 18 members, FGFs 1–10 and FGFs 16–23 (Beenken & Mohammadi 2009). Not all members of the FGF family have the potential to signal, but those that do exert their effects by interacting with four different receptors (FGFR1–4) to activate signal transduction pathways, such as the MAPK cascade, and stimulate mitogenesis, differentiation, and cell migration. FGFs are thus important regulators of multiple developmental processes (Yamaguchi & Rossant 1995). Although the role of many members of the FGF family in regulating fetal development has yet to be documented, it is apparent that both FGFR1 and FGF2 are important mediators of fetal growth (Tables 1–3). While FGFR1-deficient mice display severe growth restriction *in utero* (Deng *et al.* 1994), studies in human pregnancy reveal that maternal and cord serum levels of FGF2 positively correlate with fetal weight (Hill *et al.* 1995, Grissa *et al.* 2010). Interestingly, the effect on fetal growth was also accompanied by alterations in placental growth suggesting that FGF2 may exert its effects by influencing placental development. Recent studies support such a role; each of the FGFRs is expressed in the human placenta (Table 4); FGFR1 and FGFR3 are expressed only within the villous stroma, whereas FGFR2 and FGFR4 are expressed both within the villous stroma and in the trophoblast (Anteby *et al.* 2005) suggesting that these receptors may mediate the responsiveness of trophoblast to the growth-promoting effects of FGFs. Indeed, studies both in mice and in human placental tissue have demonstrated that FGF4 acts upon FGFR2 within trophoblast stem cells (in mice (Tanaka *et al.* 1998)) and in the cytotrophoblast (in humans (Baczyk *et al.* 2005)) to regulate the proliferation and differentiation of these cells within the developing placenta. There are few reports relating to FGF regulation of extravillous trophoblast invasion, though FGF10 appears to be stimulatory (Natanson-Yaron *et al.* 2007).

## Platelet-derived growth factors

The PDGFs A–C and their receptors PDGFRα and PDGFRβ have been shown to promote cellular responses such as proliferation, survival, and migration, thus they are important mediators of mammalian development (Hoch & Soriano 2003). Although reports of the role of PDGF in regulating fetal growth are limited (Tables 1–3), a recent study demonstrates that the maternal serum PDGFB level is enhanced in mothers suffering with gestational diabetes with macrosomic babies (Grissa *et al.* 2010), and it has been reported that placental levels of PDGFRα are reduced in FGR placentas (Jarvenpaa *et al.* 2007). In the human placenta (Table 4), PDGFRα/β is expressed within the syncytiotrophoblast and the villous cytotrophoblast (Kita *et al.* 2003); this localization together with reduced expression in FGR placentas suggests that signaling via PDGFRα may regulate trophoblast proliferation in the human placenta. At present, there are no direct reports of the role of PDGF/PDGFR signaling in the regulation of human villous, or extravillous, trophoblast function. Studies in mice do, however, support a developmental role for the PDGFR system in the placenta (Ohlsson *et al.* 1999, Looman *et al.* 2007). In mice, deletion of the gene encoding PDGFB or PDGFRβ results in multiple defects in placental development, including decreased trophoblast proliferation (Ohlsson *et al.* 1999), while an activating mutation in PDGFRβ induces hyperproliferation in the labyrinth and in the chorionic plate (Looman *et al.* 2007).

## Signaling molecules important for mediating actions of maternal growth factors in the placenta

Taken together, these studies all suggest that it should be possible to improve placental function by enhancing the response to maternal hormones. For some, but not all, of the growth factors, supplementing maternal levels could be of therapeutic benefit. However, growth factor receptors have a body-wide distribution, and many of their ligands are known

to promote tumorigenesis, thus maternal systemic administration is unlikely to be without side effects. Instead, other mechanisms to promote growth factor actions within the placenta should be explored; we suggest that methods to specifically target receptors and/or molecules within the placenta are more likely to prove beneficial.

Despite activation of their specific receptors, the downstream effect of the different growth factors is mediated by inducing activation/phosphorylation of common complex signaling cascades such as the phosphoinositide 3-kinase (PI3K) pathway or the MAPK (also termed extracellular signal-related kinase 1/2 (ERK1/2)) pathway (Fig. 2; Vincent & Feldman 2002). *In vivo*, the level of phosphorylation within these pathways is regulated by the opposing actions of protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs). While PTKs catalyze phosphorylation, PTPs are responsible for dephosphorylation. PTKs, PTPs, and their corresponding substrates are integrated within elaborate signaling networks that are essential for regulating many cellular events such as growth, differentiation, metabolism, gene transcription, and survival. These processes are all essential for mediating placental development and function, but until recently the importance of PTKs and PTPs in mediating growth factor action, and consequently normal placental development was unclear.

### *MAPK pathways*

MAPKs are an evolutionarily conserved group of enzymes that were first identified as mitogen-stimulated kinases in the late 1980s/early 1990s (Pearson *et al.* 2001) and are now known to be major components of pathways controlling many cellular events. All eukaryotic cells possess multiple MAPK pathways that are activated in response to a wide variety of ligands acting through multiple receptors; these include growth factor receptors such as IGF1R, EGFR, and PDGFR. In mammals, the MAPK cascades can be divided into four distinct groups, MAPK (ERK1/2), c-jun N-terminal kinase (JNK), p38 MAPKs, and the big MAPK, or ERK-5 cascades (Pearson *et al.* 2001).

Evidence for the involvement of ERK in placental development and subsequent fetal growth comes from studies

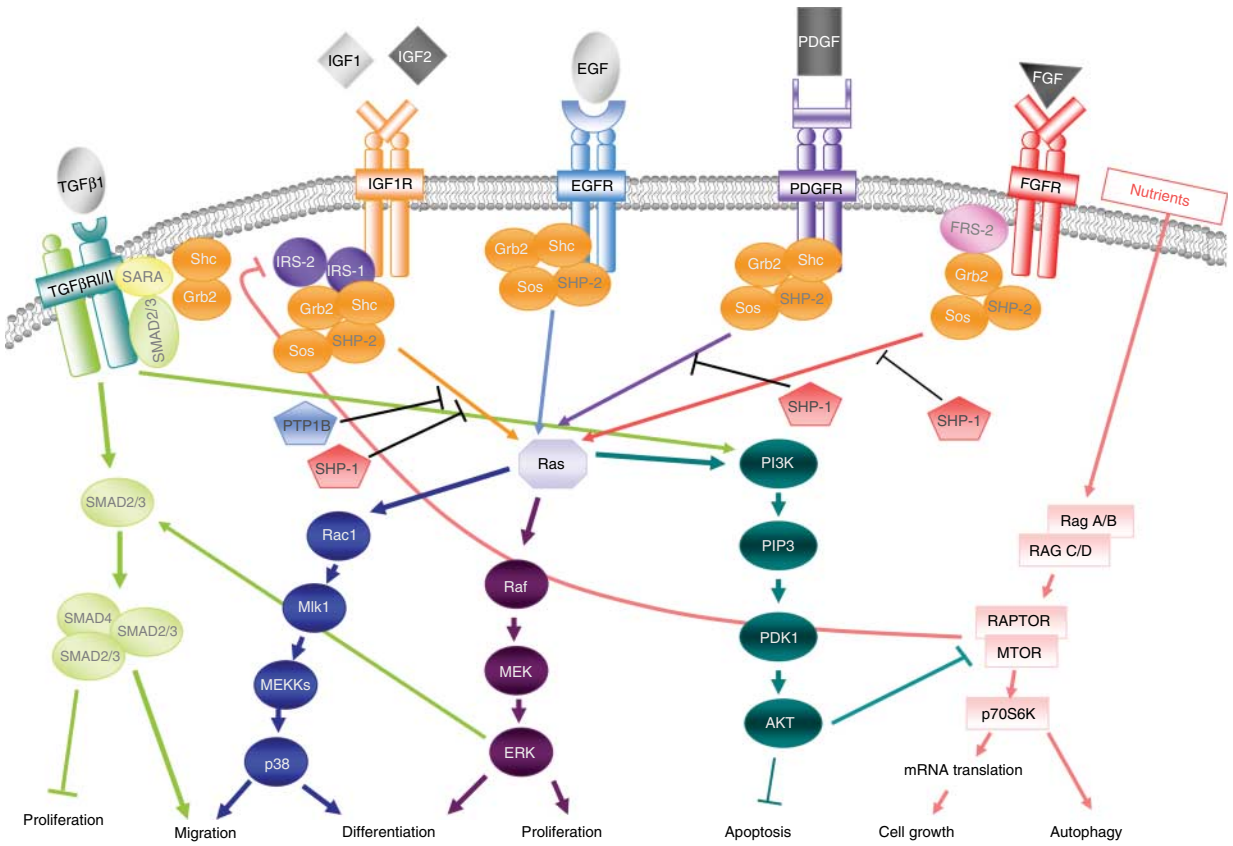


**Figure 2** Schematic diagram of growth factor-mediated signaling cascades TGFβ1, IGF1 and IGF2, EGF, PDGF, and FGF all bind to their cognate receptors thereby inducing receptor autophosphorylation and recruitment of various scaffolding proteins. This results in activation of PI3K and MAPK (ERK) pathways via a sequence of phosphorylation events resulting in transcription of target genes involved in regulating cellular events such as proliferation and survival.

in mice. Although ERK-1-deficient mice do not exhibit altered growth, mutation within the ERK-2 locus results in failure to form the mature trophoblast leading to embryonic lethality early in mouse development (Saba-El-Leil *et al.* 2003). Furthermore, ERK-2 knockout mice that have been rescued by the transgenic expression of ERK-2 are much smaller than their wild-type littermates due to abnormal placental development, though when trophoblast function is restored by generating chimeras in which placental trophoblast expression of ERK-2 is normal, embryos grow appropriately, demonstrating the importance of ERK-2 for normal placental development and, consequently, fetal growth (Hatano *et al.* 2003).

In the human placenta, ERK1/2 are expressed in the villous trophoblast (Kita *et al.* 2003), and they have been shown to regulate the differentiation of isolated primary cytotrophoblasts into syncytia (Daoud *et al.* 2005). Many studies demonstrate that activation of the MAPK pathway can be achieved in trophoblast by multiple growth factor receptors and their ligands. EGFR, TGFβR, and IGF2R regulate trophoblast invasion and migration (McKinnon *et al.* 2001, Qian *et al.* 2004) via the MAPK pathway, and we have reported that TGFβ1 (via TGFβRI/II)-induced cytotrophoblast proliferation and IGF-induced cytotrophoblast proliferation and differentiation (syncytial regeneration) occur via the MAPK pathway (Forbes *et al.* 2008, 2010*c*).

It is generally assumed that ERK1/2 is the major pathway activated by growth factors and other mitogenic stimuli, while JNK and p38 MAPK predominantly respond to stress such as osmotic stress and cytokines (Pearson *et al.* 2001). While a role for p38 in regulating stress responses has been well documented in the placenta (Renaud *et al.* 2009), it is now apparent that the p38 MAPK pathway is also an important mediator of growth factor signaling in the placenta. It is required for trophoblast differentiation and fusion in response to different mitogenic factors including serum (Daoud *et al.* 2005) and EGF (Johnstone *et al.* 2005*b*), EGF-induced trophoblast survival (Johnstone *et al.* 2005*a*, Humphrey *et al.* 2008) and extravillous trophoblast motility (LaMarca *et al.* 2008). Furthermore, p38α has been shown to be essential for murine placental development (Adams *et al.* 2000, Mudgett *et al.* 2000), and in humans phosphorylation (and activation) of p38 is reduced in FGR placentas (Laviola *et al.* 2005).

### *PI3K/AKT pathway*

In other tissues, activated growth factors recruit and phosphorylate a number of adaptor molecules and kinases leading to the activation of PI3K/AKT (also known as protein kinase B) and downstream phosphorylation cascades. AKT has been reported to regulate rodent placental development and fetal growth (Chen *et al.* 2001, Yang *et al.* 2003), and there is reduced translation of AKT in human FGR placentas (Yung *et al.* 2008, Scifres & Nelson 2009). As detailed above, one of the key regulators of placental growth is the IGF axis, and there are many studies demonstrating that the PI3K/AKT pathway mediates IGF responsiveness in the placenta. In a dexamethasone-induced murine model of FGR, reduced levels of IGF2 are accompanied by a significant reduction in levels of phosphorylated AKT (Ain *et al.* 2005), and in first trimester placental explants, AKT mediates IGF-induced trophoblast survival (Forbes *et al.* 2008). Further evidence to suggest that the PI3K pathway may be important in mediating IGF signaling events in the placenta comes from studies involving the mechanistic target of rapamycin (MTOR) pathway, which can be activated by phosphorylated AKT to promote cell growth (Levine *et al.* 2006) or can be regulated by nutrient-sensing signaling pathways (Fig. 2). Studies demonstrating that MTOR acts as a nutrient sensor to promote proliferation of immortalized human trophoblast cells (Wen *et al.* 2005), and that insulin- and IGF1-mediated amino acid transporter activity is mediated by the MTOR pathway in primary human trophoblast cells (Roos *et al.* 2009) support this hypothesis and suggest that MTOR may co-ordinate nutrient and growth factor signals to regulate normal placental development.

In addition to regulating events downstream of IGF1R, the PI3K pathway is also an important mediator of other growth factor responses in the placenta. EGF promotes trophoblast proliferation and cell survival by stimulating PI3K/AKT pathway (Johnstone *et al.* 2005*a*, Moll *et al.* 2007), while in placental stromal cells, the PI3K/AKT pathway is required for FGF2 and vascular endothelial growth factor-stimulated endothelial cell proliferation (Wang *et al.* 2009). It is now emerging that PI3K/AKT may also play additional roles within the placenta by regulating expression of leptin (Gambino *et al.* 2010), a known mediator of trophoblast proliferation and survival (Magarinos *et al.* 2007).

### *Tyrosine phosphatases*

In almost all cells, growth factor-induced activation of the PI3K and MAPK pathways is regulated by PTPs. PTPs were initially thought to be composed of a small number of non-specific 'house-keeping' enzymes whose only function was to reverse the action of PTKs. However, PTPs are now recognized as a large family of enzymes, which have structural diversity and complexity equivalent to that of the PTKs (Neel & Tonks 1997). The structural complexity of PTPs enables them to interact with a number of different proteins allowing them to exert both positive and negative effects on signaling pathways; they therefore play crucial roles in a variety of mammalian tissues and cells.

Although the mRNA for a number of PTPs is expressed at high levels within the human placenta (Norris *et al.* 1997), the function of PTPs at the maternal–fetal interface was relatively unexplored until recently. One PTP, PTP-1B, was first isolated from human placental tissue (Tonks *et al.* 1988) and has since been reported to be expressed at the protein level in the syncytiotrophoblast (Stenzinger *et al.* 2008). In other systems, it regulates insulin and IGF signaling (Koren & Fantus 2007), but its function in the

placenta is currently unknown. Another phosphatase that appears to be involved in regulating placental development is MAPK phosphatase (MKP)-4. Transgenic mice which have a specific deletion of MKP-4 have abnormal placental development, and all mice die *in utero* (Christie *et al*. 2005). MKP-4 functions to regulate the activation of the MAPK pathway, and since this pathway is integral for human placental development and mediating signals from the multiple growth factors, it is possible that this phosphatase may also function to regulate growth factor-induced signaling events in the placenta.

The majority of work examining the role of PTPs within the placenta thus far has focused on the SH-2 domain containing phosphatase, SHP-2. SHP-2 is a ubiquitously expressed intracellular PTP first cloned in 1992 (Adachi *et al*. 1992). Since then, SHP-2 has been implicated in the regulation of diverse intracellular signaling pathways, including those initiated by ligands such as insulin, IGFs, EGF, PDGF, and FGF (Chong & Maiese 2007). When SHP-2 is truncated, mice have severe developmental abnormalities and subsequently die at mid gestation (Saxton *et al*. 1997). It is now established that trophoblast stem cells in these mice fail to proliferate and survive in response to essential growth factors such as FGF4 (Yang *et al*. 2006) suggesting that the effects on fetal development are caused by the effect of SHP-2 on the placenta (Yang *et al*. 2006). We have now established that SHP-2 is also important for regulating placental development in humans. SHP-2 is highly abundant within the cytotrophoblast and regulates IGF-induced proliferation by mediating the activation of multiple components of the MAPK and PI3K pathways (Forbes *et al*. 2009). Interestingly, SHP-2 is absent from the terminally differentiated syncytiotrophoblast. It has been reported that pan-PTP inhibition induces differentiation and fusion in a trophoblast cell line (Vargas *et al*. 2008), thus a possible explanation for the absence of SHP-2 in the syncytium is that SHP-2 negatively regulates trophoblast differentiation and is therefore reduced prior to differentiation and fusion; however, this remains to be established.

SHP-1 is a structurally similar PTP to SHP-2, but while SHP-2 can have both positive and negative actions, the role of SHP-1 is predominantly as a negative regulator of cellular events (Neel *et al*. 2003) including those activated by FGF2 (Seo *et al*. 2008), IGF1 (Tenev *et al*. 1997), and PDGF (Yu *et al*. 1998). Mice with an inactivating mutation of SHP-1 have enhanced cellular proliferation (Shultz *et al*. 1993, Tsui *et al*. 1993), and it is now emerging that SHP-1 can negatively regulate activation of the MAPK cascade (Zatelli *et al*. 2005). *SHP-1* mRNA is expressed within the placenta (Norris *et al*. 1997) and is highly abundant both within the cytotrophoblast and within the villous stroma in the first trimester human placenta (Forbes *et al*. 2010*a*), thus suggesting a potential role in regulating cytotrophoblast function. Indeed, we now have evidence that SHP-1 inhibits cytotrophoblast proliferation by negatively regulating multiple receptor tyrosine kinases (Forbes *et al*. 2010*b*).

### *Targeting intracellular signaling molecules to improve placental growth*

We have discussed the role of maternal growth factors in regulating villous trophoblast turnover, and it is apparent that all of these growth factors have similar roles within the placenta. Although each ligand binds to distinct receptors on the cell surface, each receptor initiates common intracellular signaling cascades through the action of both kinases and phosphatases, and there are studies demonstrating that the expression of these proteins is essential for growth factor responses in the normal human placenta. The placental expression of numerous proteins within these cascades is altered in fetal growth complications. We therefore propose that instead of supplementing maternal growth factor levels, the greatest therapeutic benefits in pregnancies complicated by altered fetal growth will arise by developing mechanisms to specifically manipulate the expression/activation of signaling molecules which are common to multiple growth factor receptors within the placenta.

## Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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