Placenta xxx (2018) xxx-xxx

Contents lists available at ScienceDirect

Placenta

journal homepage: www.elsevier.com

Regulating needs: Exploring the role of insulin-like growth factor-2 signalling in materno-fetal resource allocation

Amanda Nancy Sferruzzi-Perri

Centre for Trophoblast Research, Department of Physiology, Development and Neuroscience, University of Cambridge, Cambridge, CB2 3EG, UK

ARTICLE INFO

Article history:
Received 24 November 2017
Received in revised form 8 January 2018
Accepted 10 January 2018
Available online xxx

Keywords:
IGF
Placental nutrient transport
Oxygen supply
Fetal growth
Pregnancy
Signalling
Nutrition
Hypoxia
Environmental manipulation

ABSTRACT

During pregnancy, the fetus requires nutrients supplied by the mother to grow and develop. However, the mother also requires sufficient resources to support the pregnancy, as well as, to maintain her health. Failure to regulate resource allocation between the mother and fetus can lead to pregnancy complications with immediate and life-long consequences for maternal and offspring health. This review explores the role of insulin-like growth factor (IGF)-2 in regulating materno-fetal resource allocation, particularly via its regulation of placental development and function.

1. Introduction

For a successful pregnancy outcome, nutrients must be partitioned correctly between the fetus for growth and development, and the mother to maintain the pregnancy and support lactation. Failure to achieve this nutrient balance can lead to pregnancy complications, such as abnormal birth weight and gestational diabetes. Combined, these complications affect >12% of pregnancies in developed nations like the UK [1] and are associated with immediate and life-long consequences for health of the mother and child. Altered nutrient and oxygen supply *in utero* leads to permanent changes in the development and function of individual fetal organs, and is associated with cardiovascular and metabolic dysfunction in offspring in later life [2,3]. In addition, maternal metabolic mal-adaptations during pregnancy can compromise the success of future pregnancies, and increase the risk of metabolic diseases, such as type 2 diabetes in the mother in later life [4]. Thus, understanding the mechanisms governing maternal-fetal resource allocation is important for pregnancy success and life-long health of both the mother and baby.

The main determinant of resource allocation during pregnancy is the placenta. It constitutes the interface between the mother and fetus that controls nutrient and oxygen transfer. The placenta responds to nutritional and metabolic signals in the mother by altering its structure and function and, thereby, appears to link maternal perturbations to changes in fetal resource supply and growth [5,6]. However, the placenta is not a passive organ; it is also able to adapt its transport capacity in response to fetal nutrient demand signals, as well as, to maternal signals of nutrient availability, thereby ensuring optimal allocation of available resources [5–8]. Moreover, the placenta signals fetal needs to the mother, via its secretion of hormones which affect maternal metabolism and thus, the supply of nutrients for fetal growth [5]. This review examines the role of the fetal growth factor, insulin-like growth factor (IGF)-2 in controlling materno-fetal resource allocation, particularly via its modulation of placental phenotype. The data discussed are largely from mice; a recently published review highlights the role of IGF2 in placental resource allocation in additional species, including the human [9].

The mouse, like the human, displays an invasive, haemochorial placenta that forms under similar genetic control [10]. However, there are a few differences between mice and humans that should be noted. In mice, the function of the yolk sac placenta persists until term and the placental exchange interface is labyrinthine rather than villous, compared to human. In mice, there is a distinct endocrine junctional zone, which is not present in the human placenta and there are differences in the types of hormones expressed between the two species [11,12]. Moreover, the mouse is a litter bearing species and the level of constraint on the mother to provide resources during pregnancy may be higher than in humans that normally have one

Abbreviations: IGF, insulin-like growth factor; IGF1R, type 1 IGF receptor; IGF2R, type 2 IGF receptor; IGFBP, IGF binding protein; INSR, insulin receptor; Jz, junctional zone; Lz, labyrinthine zone; PI3K, phosphoinositol 3-kinase

Email address: ans48@cam.ac.uk (A.N. Sferruzzi-Perri)

https://doi.org/10.1016/j.placenta.2018.01.005
0143-4004/

baby [13]. However, both genetic and environmental manipulations have been undertaken in mice, which are beneficial in providing insight into the mechanisms governing materno-fetal resource allocation in mammals.

1.1. Insulin-like growth factor-2 (IGF2)

IGF2 is a small (~7.5 kDa) anabolic polypeptide that binds to three cell surface receptors: the type 2 IGF receptor (IGF2R), the type 1 IGF receptor (IGF1R) and the insulin receptor (INSR), with decreasing affinity [14]. The mitogenic, pro-survival and metabolic actions of IGF2 are thought to be principally mediated through binding to the IGF1R, which leads to activation of the phosphoinositide-3 kinase/protein kinase A (PI3K/AKT) and mitogen-activated protein kinase (MAPK) signalling pathways [9]. In contrast, interaction of IGF2 with IGF2R results in its internalisation and degradation or activation of G-protein-coupled signalling [15]. Although, the specific conditions that determine whether IGF2 binding to the IGF2R results in its degradation or signalling, require elucidation. A family of binding proteins (IGFBPs) and IGF-related binding proteins modulate the accessibility of IGF2 to its receptors [9].

Expression of the *Igf2* gene is controlled by parental imprinting, with only the paternal allele expressed in the mouse [16]. The *Igf2* gene has multiple promoters, from which a transcript specific to the placenta, *Igf2P0,* originates in mice [17]. Recent work has shown this is due the repression of the *Igf2P0* transcript in the embryo by a zinc-finger protein, ZFP568 [18]. There is also evidence that the transcription factor, Zac1, regulates *Igf2* transcript expression in mice during prenatal development [19]. Multiple antisense transcripts for the *Igf2* gene (*Igf2as*) have also been reported to expressed in mice, albeit from the complementary DNA strand [17].

1.2. IGF2 expression at the feto-maternal interface

Components of the IGF2 system are expressed by the mouse conceptus during the early stages of development (Fig. 1). IGF2 is expressed from the 2-cell stage [20], and by implantation (~day 4 of gestation), it is co-localised with IGF1R and/or IGF2R in the cell lineages that will go on to form the fetus and placenta [21–23]. In particular, from day 5.5–6.5, IGF2 and IGF1R are abundantly expressed in the developing embryo, the extraembryonic ectoderm, and the ectoplacental cone [22]. Transcripts for *Igf2* and its receptors are also detected in the yolk sac placenta on day 9.5 of gestation [24]. Later, when the definitive mouse placenta is formed (~day 10 of gestation), IGF2 and IGF1R are expressed by the syncytiotrophoblast in the transport labyrinthine zone (Lz) and enriched in the glycogen cells in the endocrine junctional zone (Jz), although they are also present in the spongiotrophoblast and giant cells [25,26]. Particularly during vascularisation, IGF2 is highly expressed by the chorionic mesoderm and Lz fetal vessels [25,27]. IGF2 is also abundantly expressed by the endoderm and mesoderm of the yolk sac placenta at day 12.5 of gestation [27]. The *Igf2P0* transcript appears to be specifically expressed by cell lineages in the Lz, at least at day 12 of pregnancy [28]. *Igf2as* transcripts have been detected during the early stages of embryonic development, although their spatial expression in the definitive placenta and yolk sac remains to be determined [24,29]. IGF2R is also expressed by the embryo and trophoblast cell lineages post-implantation [23]. However, at around day 10.5, IGF2R expression appears to be mainly confined to the vasculature in the Lz, and trophoblast lineages in the Jz [22,26]. INSR is also expressed by the mouse placenta and yolk sac in early and/or the late stages of development [23,24,30], although its specific localisation is unknown. The IGFBPs are predominantly expressed by the decidua, although lower expression levels of specific IGFBPs have been reported for the chorionic mesoderm, Lz, Jz and yolk sac placenta [24,27,31,32]. Combined, these data suggest that IGF2 may interact with IGF2R to drive Lz vascularisation, IGF1R to promote formation and function of the syncytiotrophoblast and both IGF receptors to control Jz differentiation and yolk sac function during mouse development. Moreover, such interactions may be fine-tuned by the IGFBPs.

1.3. IGF2 and its importance for feto-placental phenotype and resource allocation

Genetic studies in mice have supported the important role of IGF2 as a fetal growth factor via its direct anabolic actions within the fetus, and by its modulation of placental supply capacity (Fig. 2). For instance, *Igf2* over-expression causes placental and fetal overgrowth [33], whereas *Igf2* gene deletion reduces feto-placental weight from early in gestation [34,35]. These changes relate to alterations in placental Lz (composition, surface area and/or barrier thickness; which determine nutrient and/or oxygen transfer) and Jz formation (glycogen cells), and a decrease in placental nutrient transport, passive permeability and supply efficiency [33,36–40]. Deleting the Lz-exclusive *Igf2P0* transcript in mice, which leaves the other placental transcripts and fetal expression of *Igf2* intact, also impairs growth of both placental zones from early in development, and reduces the passive permeability of the placenta, as well as, fetal

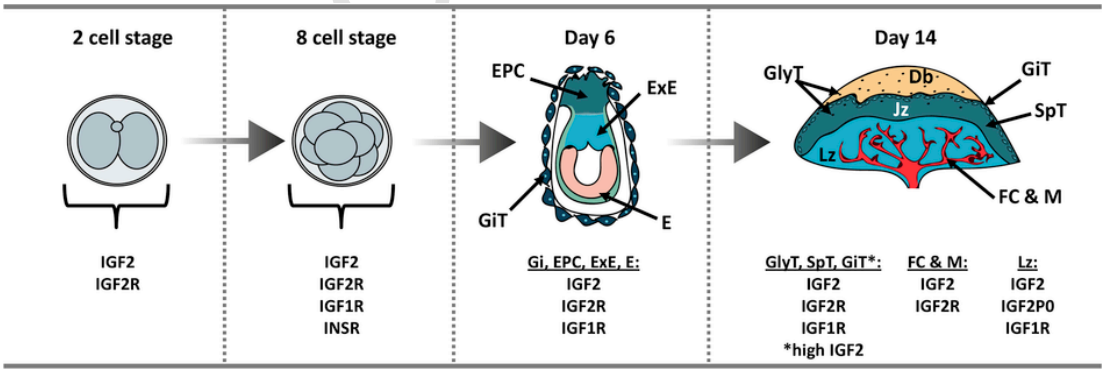

Fig. 1. Expression of IGF2 and the receptors it can bind by the mouse conceptus during development. Data shown for day 14 of pregnancy are inferred from studies performed on samples collected from days 10.5 until day 18.5 of pregnancy. E, embryo; EPC, ectoplacental cone; ExE, extraembryonic mesenchyme; FC, fetal capillaries; GiT, giant cells, GlyT, glycogen cells, SpT, spongiotrophoblast; Lz, labyrinthine zone. Data are from Refs. [20–23,25–28]. Note, IGF2 is also abundantly expressed by the endoderm and mesoderm of the yolk sac during gestation.

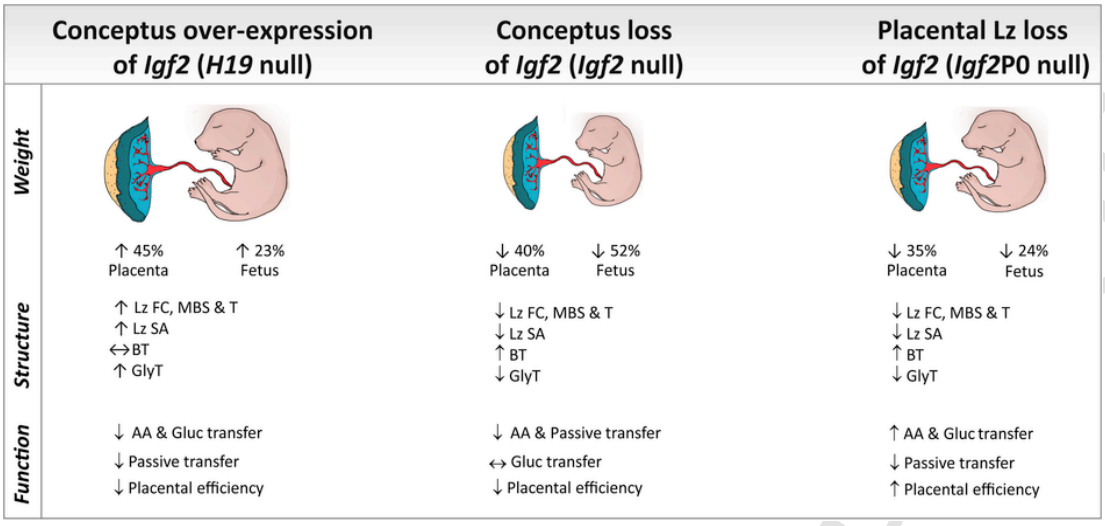

Fig. 2. Impact of genetically manipulating the expression of *Igf2* on fetal growth and placental development and transport function. AA, amino acid; BT, interhaemal membrane barrier thickness (inversely related to the diffusion of molecules like oxygen), FC, fetal capillaries; Glu, glucose; GlyT, glycogen cells; Lz, labyrinthine zone; MBS, maternal blood spaces; SA, surface area; T, trophoblast. Data are from Refs. [28,33,37–41].

growth [28,39]. As the *Igf2P0* transcript accounts for ~10% of total *Igf2* transcripts in the mature mouse placenta [28], these findings highlight that the *Igf2P0* transcript plays a disproportionately important role in promoting fetal and placental growth.

The *Igf2P0* deficient placenta also adapts its nutrient transport characteristics to help maintain fetal growth. Fetal growth is not restricted until late gestation and to a lesser extent as predicted by the reduced size and passive permeability of the *Igf2P0* null [28,37]. This is because the *Igf2P0* null placenta is able to partially compensate for these defects by up-regulating its capacity for glucose, amino acid and calcium transport during pregnancy [28,41,42]. This increase in placental supply efficiency is associated with enhanced expression of glucose and System A amino acid transporters, as well as, the intracellular calcium-binding protein, calbindin-D9K by the *Igf2P0* mutant placenta. Adaptations in glucose and amino acid transport, however, do not occur in the complete *Igf2* null that lacks both placental and fetal *Igf2* [37]. The impact of *Igf2* deficiency on the capacity of the yolk sac to provide maternal nutrients for fetal growth, although, remains to be explored. Genetic manipulation of *Igf1r*, *Igf2r* and *Insr* also affects feto-placental phenotype, which has previously been summarised [9]. Taken together, these data emphasize an interplay between placental *Igf2* transcripts and fetal IGF2 in regulating placental nutrient allocation to the fetus. The available data also suggest that IGF2 may play a role, directly or indirectly, in adapting placental transport capacity during development.

1.4. IGF2 in the environmental modulation of placental resource supply to fetal growth

Mechanisms adapting placental transport capacity are likely to be particularly important when maternal conditions are not favourable for fetal nutrient supply. Undernutrition during pregnancy is common in many developing countries and is the main cause of pregnancy complications such as low birth weight [43]. In mice, undernutrition (20% reduction in food intake from day 3 of pregnancy) leads to a down-regulation of *Igf2P0* expression and PI3K signalling in association with reduced placental weight in early gestation [43,44]. However, fetal growth is only restricted just prior to term in undernourished dams [43]. Fetal growth is preserved until this time through the maintenance of Lz formation in early pregnancy, and an adaptive up-regulation of amino acid transport in late gestation by the growth restricted, undernourished wildtype placenta [43]. These adaptations depend on *Igf2P0* expression by the undernourished placenta, as Lz development is defective from early in gestation and there is no adaptive increase in amino acid transport near term in the small *Igf2P0* deficient placenta in response to maternal undernutrition [44]. The morphological and functional failure of the *Igf2P0* null placenta to adapt to undernutrition, results in an earlier onset and more severe reduction in fetal size, as compared to that seen with the wildtype placenta. Thus, the data suggest that the placental-specific transcript of the *Igf2* gene is involved in placental adaptations to undernutrition.

IGF2 may also play a role in the adaptation of placental resource supply in pregnancies challenged by an obesogenic diet. In many developed countries, women of reproductive age obtain a high proportion of their energy intake from fat and/or sugar [30]. These dietary habits contribute to the increasing number of women who gain excess weight and develop gestational diabetes during pregnancy. In mice, the consumption of an obesogenic diet containing high sugar and high fat (5-times sugar and 3-times fat of control chow; HSHF) from day 1 of pregnancy compromises maternal insulin sensitivity, glucose tolerance and glucose production [45]. Furthermore, fetal growth, placental size and Lz development is reduced in early gestation by a HSHF diet [30]. However, by term, fetal weights are no longer reduced, despite the placenta remaining small and morphologically defective [30]. The normalisation of fetal growth in late gestation is associated with an up-regulation of glucose and amino acid transfer by the placenta to the fetus in HSHF dams earlier in pregnancy [30]. This increase in placental supply capacity is coupled with an enhanced expression of the System A amino acid transporter, *Slc38a2,* and glucose transporter, *Slc2a3*. It is also associated with an increase in *Igf2P0* transcript expression and PI3K signalling in the placenta of dams fed the HSHF diet. Collectively, these data suggest that in response to an obesogenic diet that disrupts maternal metabolism, the placenta adapts its phenotype to help meet fetal nutrient demands for growth near term. Moreover, these adaptations are associated with changes in IGF2 signalling in the placenta.

Recent evidence suggests that IGF2 signalling may also be involved in altering placental supply capacity in response to hypoxia during pregnancy. Hypoxia is a common feature of compromised

human pregnancies at sea level with adverse outcomes for the infant. Moreover, hypoxia is a major cause of fetal growth restriction in pregnancies at high altitude [46]. In mice, reducing maternal inspired oxygen to 13% for five days prior to term, leads to an increase in placental *Igf2P0* expression and PI3K signalling in association with greater Lz vascular density, a thinner barrier to diffusion of molecules like oxygen, increased glucose transport and only a marginal (5%) reduction in fetal growth [46]. In contrast, reducing maternal inspired oxygen to 10% for the same duration does not induce beneficial changes in placental *Igf2P0* expression and PI3K signalling, nor lead to an increase in Lz vascularisation or glucose transport. In contrast, 10% hypoxia results in a thicker trophoblast barrier to diffusion, diminished placental amino acid transport, and a four times greater reduction (21%) in fetal growth [46]. Taken together, these data suggest that there is a threshold between 13% and 10% maternal inspired oxygen, at which the placenta can no longer optimise fetal nutrient and oxygen supply and fetal growth in late pregnancy. Furthermore, changes in placental supply capacity with hypoxia appear to relate to the level of IGF2 signalling in the placenta.

Similar relationships between IGF2 signalling and placental supply capacity have been reported in response to other maternal challenges that affect conceptus development [9]. For instance, elevating the concentration of the stress hormone, corticosterone in mouse dams in late pregnancy diminishes placental PI3K signalling and compromises placental size, Lz morphology, amino acid supply capacity and fetal growth [47,48].

Taken together, the available data demonstrate that an environmental challenge, which affects the ability of the mother to provide nutrients and oxygen to fetal growth, is associated with changes in placental IGF2 signalling, morphology and functional capacity (Table 1). Moreover, the timing, nature and type of challenge during pregnancy determine the specific placental response elicited. However, irrespective of the insult, whenever placental resource allocation is altered, there is a change in IGF2 signalling in the placenta (Table 1). Thus, IGF2 appears to act as an environmental sensor, driving changes in placental phenotype to optimise the allocation of resources in the prevailing environment [9]. However, functional studies combining environmental and genetic manipulations in mice are needed to more precisely determine the casual relationships between changes in placental IGF2, resource allocation and fetal growth (as done previously for undernutrition and the *Igf2P0* null [44]). Future studies are also required to identify the mechanisms by which *Igf2* expression by the placenta may be modified by the gestational environment.

Table 1
A summary of the impact of maternal environmental manipulations on placental phenotype and fetal weight in mice.

	Maternal challenge				
	Undernutrition	Obesogenic diet	13% hypoxia	10% hypoxia	Excess corticosterone
Placental Lz development	Initially preserved ↓ late in gestation	↓	↑	↓	↓
Placental transport	↑ AA	↑ AA & glucose ↓ oxygen	↑ glucose & oxygen	↓ AA & oxygen	↓ AA
Placental IGF2–PI3K signalling	↓[a]	↑	↑	↓	↓
Fetal weight	↔ early in gestation ↓ 14% late in gestation	↓ 10% early in gestation ↔ late in gestation	↓ 5%	↓ 21%	↓ 20%

[a] *Igf2P0* required for the structural and functional adaptations to maternal undernutrition. Data are from Refs. [30,44,46–48]. Oxygen transfer is inferred from the interhaemal membrane barrier thickness. AA, amino acid.

1.5. Maternal versus fetal signalling in the regulation of placental resource allocation

IGF2 is not only highly expressed in the placenta, but is abundant in the fetal and maternal circulation during mouse pregnancy [49,50]. Thus, adaptations in placental resource allocation may also be driven by IGF2 signalling in the fetus or the mother, or both. In adult tissues, the PI3K catalytic isoform, p110α is largely responsible for mediating the metabolic effects of anabolic hormones, like IGF2 [51]. Studies in mice using genetic manipulation of p110α have therefore, started to provide insight into the role of signalling in the fetus *versus* in the mother, in determining specific placental phenotypes. In mice, genetically inactivating p110α activity by 50% ($p110\alpha^{D933A/+}$; α/+) in the fetus, reduces placental size and Lz formation (decreases in Lz vascularisation, surface area and an increase in the barrier to diffusion), in association with impaired fetal growth [52]. However, despite the compromised morphology, the placenta adapts functionally by increasing the supply of glucose and amino acid to the fetus in α/+ mutants. This increase in placental supply capacity is more pronounced near term and relates to an improved growth trajectory of α/+ fetuses when compared with wildtypes. These data suggest functional adaptation of placental nutrient allocation in response to a deficiency in fetal p110α signalling.

Placental resource allocation also responds to a deficiency of p110α signalling in the mother. In α/+ mouse dams, placental weight and Lz formation is increased (larger surface area and reduced barrier to diffusion, depending on the gestational age) although the placenta transports less glucose to the fetus and fetal weight is unaffected by the maternal genotype during pregnancy [52]. These maternally-driven alterations in placental phenotype appear to be related to the reduced size and altered metabolic and endocrine milieu of the α/+ dam during pregnancy [52]. Hence, there is adaptation of the placenta to match the supply capacity of the dam with a deficiency in p110α signalling. Overall, the data therefore suggest that placental resource allocation adapts in response to changes in IGF2 signalling capacity in both the fetus and mother. However, caution is warranted as little is known about the abundance of the IGF2 system components in the α/+ fetuses or dams. There is also no information available on the pathways that may compensate to improve placental transport capacity in the α/+ conceptuses. Such signalling pathways include the mechanistic target of rapamycin, general control nonrepressed 2, G-protein coupled-receptors and adenosine monophosphate-activated protein kinase which have been implicated in environmental sensing [53,54] and may drive alterations in placental transport phenotype in response to IGF2/p110α signalling deficiency.

1.6. Role of IGF2 in placental endocrine regulation of maternal resource allocation to the fetus

As previously mentioned, the placenta secretes hormones that affect the availability of nutrients in the mother for fetal growth. Moreover, IGF2 is important for the formation and function of endocrine cells in the mouse placenta (Fig. 2). It is therefore plausible that via its modulation of placental endocrine capacity, IGF2 may be involved in signalling to the mother to alter her provision of nutrients for the

fetus. Studies of wildtype dams carrying *Igf2* mutant conceptuses supports this notion. For instance, dams carrying pups with *Igf2* over-expression show increased glucose concentrations during pregnancy [55]. Furthermore, dams carrying litters of *Igf2P0* nulls show increased circulating glucose, insulin, leptin and/or corticosterone concentrations in fed and undernourished conditions [44]. Studies selectively modulating the expression of *Igf2* in placental endocrine cells are although warranted to specifically address the role of IGF2 in placental endocrine regulation of maternal-fetal nutrient allocation.

2. Summary and conclusions

In mice, IGF2 is important for controlling placental resource allocation to fetal growth via its actions on placental formation, nutrient transport and endocrine capacity during development, as well as, in response to environmental challenges (Fig. 3). Moreover, via the IGF2 signalling pathway, the placenta is able to fine-tune the supply of maternal resources to the fetus in accordance with both the fetal drive for growth and the maternal ability to supply the required nutrients during pregnancy. In human pregnancy, IGF2 is present in both the fetal and maternal circulations and the IGF2 system is widely expressed by the placenta [9,56]. It promotes the proliferation, differentiation, survival and uptake of nutrients by cultured human trophoblast and the abundance of the IGF2 system is altered in the placenta from women with poor environmental conditions (unbalanced dietary intakes, obesity, increased cortisol, residence at high altitude) and/or abnormal fetal growth during pregnancy (reviewed previously [9,56]). Therefore, IGF2 may play a similar regulatory role in controlling placental resource allocation during human pregnancy. By understanding the role of IGF2 in regulating the allocation of resources between the mother and fetus during pregnancy, the work discussed may provide novel insight into the aetiology of pregnancy complications and programming mechanisms.

Conflicts of interest

The author has no competing interests to declare.

Acknowledgements

I would like to thank the Australian National Health and Medical Research Council for a CJ Martin Fellowship, the Centre for Trophoblast Research for a Next Generation Fellowship and the Royal Society for a Dorothy Hodgkin Research Fellowship funding my past and current research featured in this review article. I would also like to acknowledge those who contributed to the work discussed, particularly Prof Abigail Fowden, Dr Miguel Constancia, Dr Owen Vaughan, Dr Barbara Musial and Dr Josephine Higgins. I would also like to thank Dr Jorge Lopez-Tello for transforming my hand-drawn figures into manuscript quality figures and Dr Hannah Yong and Dr Emily Camm for proof-reading this manuscript.

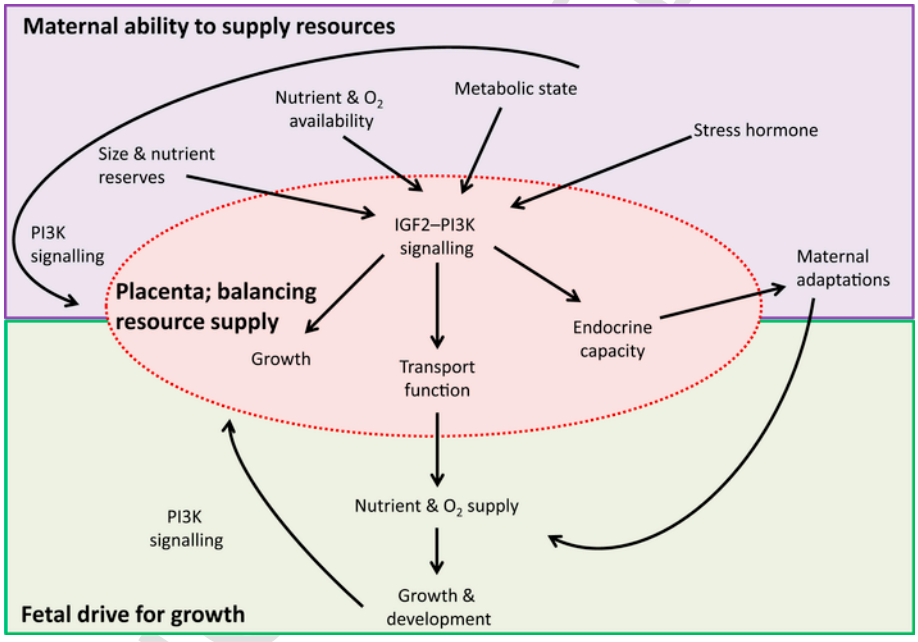

Fig. 3. The role of IGF2 signalling in the placenta and its importance for the allocation of resources between the mother and the fetus for growth.

References

[1] Statistics OfN, Birth Characteristics in England and Wales: 2014. Statistical Bulletin, 2015.

[2] A.L. Fowden, D.A. Giussani, A.J. Forhead, Intrauterine programming of physiological systems: causes and consequences, Physiology 21 (2006) 29–37.

[3] P.D. Gluckman, M.A. Hanson, C. Cooper, K.L. Thornburg, Effect of in utero and early-life conditions on adult health and disease, N. Engl. J. Med. 359 (1) (2008) 61–73.

[4] C. Kim, Maternal outcomes and follow-up after gestational diabetes mellitus, Diabet. Med. 31 (3) (2014) 292–301.

[5] A.N. Sferruzzi-Perri, E.J. Camm, The programming power of the placenta, Front. Physiol. 7 (2016) 33.

[6] P. Diaz, T.L. Powell, T. Jansson, The role of placental nutrient sensing in maternal-fetal resource allocation, Biol. Reprod. 91 (4) (2014) 82.

[7] I. Sandovici, K. Hoelle, E. Angiolini, M. Constancia, Placental adaptations to the maternal-fetal environment: implications for fetal growth and developmental programming, Reprod. Biomed. Online 25 (1) (2012) 68–89.

[8] A.L. Fowden, A.N. Sferruzzi-Perri, P.M. Coan, M. Constancia, G.J. Burton, Placental efficiency and adaptation: endocrine regulation, J. Physiol. 587 (Pt 14) (2009) 3459–3472.

[9] A.N. Sferruzzi-Perri, I. Sandovici, M. Constancia, A.L. Fowden, Placental phenotype and the insulin-like growth factors: resource allocation to fetal growth, J. Physiol. 595 (15) (2017) 5057–5093.

[10] A.M. Carter, Animal models of human placentation - a review, Placenta, Trophoblast Research 28 (Supplement 1) (2007) S41–S47.

[11] M.J. Soares, The prolactin and growth hormone families: pregnancy-specific hormones/cytokines at the maternal-fetal interface, Reprod. Biol. Endocrinol. 2 (2004) 51.

[12] D. Haig, Placental growth hormone-related proteins and prolactin-related proteins, Placenta 29 (Supplement 1) (2008) 36–41.

[13] A.L. Fowden, T. Moore, Maternal-fetal resource allocation: co-operation and conflict, Placenta 33 (Suppl 2) (2012) e11–e15.

[14] E.L. Germain-Lee, M. Janicot, R. Lammers, A. Ullrich, S.J. Casella, Expression of a type I insulin-like growth factor receptor with low affinity for insulin-like growth factor II, Biochem. J. 281 (Pt 2) (1992) 413–417.

[15] L.K. Harris, M. Westwood, Biology and significance of signalling pathways activated by IGF-II, Growth Factors 30 (1) (2012) 1–12.

[16] D. Monk, P. Arnaud, S. Apostolidou, F.A. Hills, G. Kelsey, P. Stanier, R. Feil, G.E. Moore, Limited evolutionary conservation of imprinting in the human placenta, Proc. Natl. Acad. Sci. U. S. A. 103 (17) (2006) 6623–6628.

[17] T. Moore, M. Constancia, M. Zubair, B. Bailleul, R. Feil, H. Sasaki, W. Reik, Multiple imprinted sense and antisense transcripts, differential methylation and tandem repeats in a putative imprinting control region upstream of mouse Igf2, Proc. Natl. Acad. Sci. U. S. A. 94 (23) (1997) 12509–12514.

[18] P. Yang, Y. Wang, D. Hoang, M. Tinkham, A. Patel, M.A. Sun, G. Wolf, M. Baker, H.C. Chien, K.N. Lai, X. Cheng, C.J. Shen, T.S. Macfarlan, A placental growth factor is silenced in mouse embryos by the zinc finger protein ZFP568, Science 356 (6339) (2017) 757–759.

[19] A. Varrault, C. Gueydan, A. Delalbre, A. Bellmann, S. Houssami, C. Aknin, D. Severac, L. Chotard, M. Kahli, A. Le Digarcher, P. Pavlidis, L. Journot, Zac1 regulates an imprinted gene network critically involved in the control of embryonic growth, Dev. Cell 11 (5) (2006) 711–722.

[20] T. Stojanov, S. Alechna, C. O'Neill, In-vitro fertilization and culture of mouse embryos in vitro significantly retards the onset of insulin-like growth factor-II expression from the zygotic genome, Mol. Hum. Reprod. 5 (2) (1999) 116–124.

[21] J.E. Lee, J. Pintar, A. Efstratiadis, Pattern of the insulin-like growth factor II gene expression during early mouse embryogenesis, Development 110 (1) (1990) 151–159.

[22] K.G. Pringle, C.T. Roberts, New light on early post-implantation pregnancy in the mouse: roles for insulin-like growth factor-II (IGF-II)?, Placenta 28 (4) (2007) 286–297.

[23] D.A. Rappolee, K.S. Sturm, O. Behrendtsen, G.A. Schultz, R.A. Pedersen, Z. Werb, Insulin-like growth factor II acts through an endogenous growth pathway regulated by imprinting in early mouse embryos, Genes Dev. 6 (6) (1992) 939–952.

[24] T. Cindrova-Davies, E. Jauniaux, M.G. Elliot, S. Gong, G.J. Burton, D.S. Charnock-Jones, RNA-seq reveals conservation of function among the yolk sacs of human, mouse, and chicken, Proc. Natl. Acad. Sci. U. S. A. 114 (24) (2017) E4753–E4761.

[25] R.W. Redline, C.L. Chernicky, H.Q. Tan, J. Ilan, Differential expression of insulin-like growth factor-II in specific regions of the late (post day 9.5) murine placenta, Mol. Reprod. Dev. 36 (2) (1993) 121–129.

[26] P.M. Coan, N. Conroy, G.J. Burton, A.C. Ferguson-Smith, Origin and characteristics of glycogen cells in the developing murine placenta, Dev. Dynam. 235 (12) (2006) 3280–3294.

[27] A.M. Carter, K. Nygard, D.M. Mazzuca, V.K. Han, The expression of insulin-like growth factor and insulin-like growth factor binding protein mRNAs in mouse placenta, Placenta 27 (2–3) (2006) 278–290.

[28] M. Constancia, M. Hemberger, J. Hughes, W. Dean, A. Ferguson-Smith, R. Fundele, F. Stewart, G. Kelsey, A. Fowden, C. Sibley, W. Reik, Placental-specific IGF-II is a major modulator of placental and fetal growth, Nature 417 (6892) (2002) 945–948.

[29] C. Duart-Garcia, M.H. Braunschweig, Functional expression study of Igf2 antisense transcript in mouse, Int. J. Geom. 2014 (2014) 390296.

[30] A.N. Sferruzzi-Perri, O.R. Vaughan, M. Haro, W.N. Cooper, B. Musial, M. Charalambous, D. Pestana, S. Ayyar, A.C. Ferguson-Smith, G.J. Burton, M. Constancia, A.L. Fowden, An obesogenic diet during mouse pregnancy modifies maternal nutrient partitioning and the fetal growth trajectory, FASEB 27 (10) (2013) 3928–3937.

[31] Z.K. Liu, R.C. Wang, B.C. Han, Y. Yang, J.P. Peng, A novel role of IGFBP7 in mouse uterus: regulating uterine receptivity through Th1/Th2 lymphocyte balance and decidualization, PLoS One 7 (9) (2012), e45224.

[32] M. van Kleffens, C. Groffen, D.J. Lindenbergh-Kortleve, J.W. van Neck, S. Gonzalez-Parra, N. Dits, E.C. Zwarthoff, S.L. Drop, The IGF system during fetal-placental development of the mouse, Mol. Cell. Endocrinol. 140 (1–2) (1998) 129–135.

[33] E. Angiolini, P.M. Coan, I. Sandovici, O.H. Iwajomo, G. Peck, G.J. Burton, C.P. Sibley, W. Reik, A.L. Fowden, M. Constancia, Developmental adaptations to increased fetal nutrient demand in mouse genetic models of Igf2-mediated overgrowth, FASEB 25 (5) (2011) 1737–1745.

[34] J. Baker, J.P. Liu, E.J. Robertson, A. Efstratiadis, Role of insulin-like growth factors in embryonic and postnatal growth, Cell 75 (1) (1993) 73–82.

[35] L.N. Kent, S. Ohboshi, M.J. Soares, Akt1 and insulin-like growth factor 2 (Igf2) regulate placentation and fetal/postnatal development, Int. J. Dev. Biol. 56 (4) (2012) 255–261.

[36] J.C. Matthews, M.J. Beveridge, E. Dialynas, A. Bartke, M.S. Kilberg, D.A. Novak, Placental anionic and cationic amino acid transporter expression in growth hormone overexpressing and null IGF-II or null IGF-I receptor mice, Placenta 20 (8) (1999) 639–650.

[37] M. Constancia, E. Angiolini, I. Sandovici, P. Smith, R. Smith, G. Kelsey, W. Dean, A. Ferguson-Smith, C.P. Sibley, W. Reik, A. Fowden, Adaptation of nutrient supply to fetal demand in the mouse involves interaction between the Igf2 gene and placental transporter systems, Proc. Natl. Acad. Sci. U.S.A. 102 (52) (2005) 19219–19224.

[38] D.R. Esquiliano, W. Guo, L. Liang, P. Dikkes, M.F. Lopez, Placental glycogen stores are increased in mice with H19 null mutations but not in those with insulin or IGF type 1 receptor mutations, Placenta 30 (8) (2009) 693–699.

[39] P.M. Coan, A.L. Fowden, M. Constancia, A.C. Ferguson-Smith, G.J. Burton, C.P. Sibley, Disproportional effects of Igf2 knockout on placental morphology and diffusional exchange characteristics in the mouse, J. Physiol. 586 (20) (2008) 5023–5032.

[40] M.F. Lopez, P. Dikkes, D. Zurakowski, L. Villa-Komaroff, Insulin-like growth factor II affects the appearance and glycogen content of glycogen cells in the murine placenta, Endocrinology 137 (5) (1996) 2100–2108.

[41] C.P. Sibley, P.M. Coan, A.C. Ferguson-Smith, W. Dean, J. Hughes, P. Smith, W. Reik, G.J. Burton, A.L. Fowden, M. Constancia, Placental-specific insulin-like growth factor 2 (Igf2) regulates the diffusional exchange characteristics of the mouse placenta, Proc. Natl. Acad. Sci. U.S.A. 101 (21) (2004) 8204–8208.

[42] M.R. Dilworth, L.C. Kusinski, E. Cowley, B.S. Ward, S.M. Husain, M. ConstÃ¢ncia, C.P. Sibley, J.D. Glazier, Placental-specific Igf2 knockout mice exhibit hypocalcemia and adaptive changes in placental calcium transport, Proc. Natl. Acad. Sci. U.S.A. 107 (8) (2010) 3894–3899.

[43] P.M. Coan, O.R. Vaughan, Y. Sekita, S.L. Finn, M. Constancia, G.J. Burton, A.L. Fowden, Adaptations in placental phenotype support fetal growth during undernutrition of pregnant mice, J. Physiol. 588 (Pt 3) (2010) 527–538.

[44] A.N. Sferruzzi-Perri, O.R. Vaughan, P.M. Coan, M.C. Suciu, R. Darbyshire, M. Constancia, G.J. Burton, A.L. Fowden, Placental-specific Igf2 deficiency alters developmental adaptations to undernutrition in mice, Endocrinology 152 (8) (2011) 3202–3212.

[45] B. Musial, O.R. Vaughan, D.S. Fernandez-Twinn, P. Voshol, S.E. Ozanne, A.L. Fowden, A.N. Sferruzzi-Perri, A Western-style obesogenic diet alters maternal metabolic physiology with consequences for fetal nutrient acquisition in mice, J. Physiol. 595 (14) (2017) 4875–4892.

[46] J.S. Higgins, O.R. Vaughan, E.F. de Liger, A.L. Fowden, A.N. Sferruzzi-Perri, Placental phenotype and resource allocation to fetal growth are modified by the timing and degree of hypoxia during mouse pregnancy, J. Physiol. 594 (5) (2015) 1341–1356.

[47] O.R. Vaughan, H.M. Fisher, K.N. Dionelis, E.C. Jefferies, J.S. Higgins, B. Musial, A.N. Sferruzzi-Perri, A.L. Fowden, Corticosterone alters materno-fetal glucose partitioning and insulin signalling in pregnant mice, J. Physiol. 593 (5) (2015) 1307–1321.
[48] O.R. Vaughan, A.N. Sferruzzi-Perri, A.L. Fowden, Maternal corticosterone regulates nutrient allocation to fetal growth in mice, J. Physiol. 590 (21) (2012) 5529–5540.
[49] A.N. Sferruzzi-Perri, J.A. Owens, K.G. Pringle, C.T. Roberts, The neglected role of insulin-like growth factors in the maternal circulation regulating fetal growth, J. Physiol. 589 (Pt 1) (2010) 7–20.
[50] A.N. Sferruzzi-Perri, O.R. Vaughan, A.J. Forhead, A.L. Fowden, Hormonal and nutritional drivers of intrauterine growth, Curr. Opin. Clin. Nutr. Metab. Care 16 (3) (2013) 298–309.
[51] L.C. Foukas, M. Claret, W. Pearce, K. Okkenhaug, S. Meek, E. Peskett, S. Sancho, A.J.H. Smith, D.J. Withers, B. Vanhaesebroeck, Critical role for the p110[alpha] phosphoinositide-3-OH kinase in growth and metabolic regulation, Nature 441 (7091) (2006) 366–370.
[52] A.N. Sferruzzi-Perri, J. Lopez-Tello, A.L. Fowden, M. Constancia, Maternal and fetal genomes interplay through phosphoinositol 3-kinase(PI3K)-p110a signalling to modify placental resource allocation, Proc. Natl. Acad. Sci. U.S.A. 113 (40) (2016) 11255–11260.
[53] T. Jansson, I.L. Aye, D.C. Goberdhan, The emerging role of mTORC1 signaling in placental nutrient-sensing, Placenta 33 (Suppl 2) (2012) e23–e29.
[54] A. Efeyan, W.C. Comb, D.M. Sabatini, Nutrient-sensing mechanisms and pathways, Nature 517 (7534) (2015) 302–310.
[55] C.J. Petry, M.L. Evans, D.L. Wingate, K.K. Ong, W. Reik, M. Constancia, D.B. Dunger, Raised late pregnancy glucose concentrations in mice carrying pups withtargeted disruption of H19Delta13, Diabetes 59 (1) (2010) 282–286.
[56] K. Forbes, M. Westwood, Maternal growth factor regulation of human placental development and fetal growth, J. Endocrinol. 207 (1) (2010) 1–16.