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Review: Placental homeobox genes and their role in regulating human fetal growth.

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Abstract

The regulation of fetal growth is multifactorial and complex. Normal fetal growth is determined by the genetically predetermined growth potential and further modulated by maternal, fetal, placental, and environmental factors. The placenta provides critical transport functions between the maternal and fetal circulations during intrauterine development. Formation of this interface is controlled by several growth factors, cytokines and transcription factors including homeobox genes. This review summarises our current knowledge regarding homeobox genes in the human placenta and their differential expression and functions in human idiopathic fetal growth restriction (FGR). The review also describes the research strategies that were used for the identification of homeobox genes, their expression in FGR, functional role and target genes of homeobox genes in the trophoblasts and the hormonal regulators of homeobox gene expression *in vitro*. A better understanding of molecular pathways driven by placental homeobox genes and further elucidation of signaling pathways underlying the hormone-mediated homeobox gene developmental programs may offer novel strategies of targeted therapy for improving fetoplacental growth in idiopathic FGR pregnancies.

1. Introduction

During pregnancy, the placenta is the principal site of metabolic, respiratory, excretory and endocrine action. These functions provide essential support for the growing fetus. The generation of distinct trophoblast cell types within the placenta is required to implement the complex biological processes of implantation, maternal-fetal exchange and maternal tolerance to fetal-parental antigens. Failure in any one of these functions is associated with a range of complications associated with human pregnancy disorders, including missed abortion, miscarriage, fetal growth restriction (also known as intrauterine growth restriction), and pre-eclampsia [1-3].

The placenta is derived from two major cell lineages [4,5]. Cytotrophoblast stem cells originate from the trophectoderm, the outermost epithelial cell layer of the blastocyst, which triggers attachment and implantation in the receptive maternal endometrium. Stromal cells and blood vessels of the placenta are derived from the extra-embryonic mesoderm. The cytotrophoblast stem cells differentiate into either the villous or the extravillous cytotrophoblast lineages. Villous cytotrophoblasts are found in the floating villi, which are present in the intervillous space, and these cytotrophoblasts remain attached to the villous basement membrane to form a monolayer of epithelial cells. These mononuclear cytotrophoblasts proliferate, differentiate and fuse to form the multinucleated syncytium of the definitive placenta, the syncytiotrophoblast, which covers the entire surface of the villus. The syncytium is multi-functional and its primary roles include absorption, exchange and transport of nutrients and gases from the maternal to the fetal circulation as well as the production of pregnancy hormones. The multinuclear syncytium is the primary site of endocrine activity in the placenta and secretes hormones such as human chorionic gonadotropin (hCG), human placental lactogen (hPL) and placental growth hormone (PGH), all of which are important for placental growth and/or maternal adaptation to pregnancy [6-8].

The extravillous cytotrophoblast lineage is derived from cytotrophoblast cells of the anchoring villi, which proliferate, detach from the basement membrane and aggregate into multilayered columns of non-polarised cells that rapidly invade into the uterine wall. This extravillous cytotrophoblastic invasion is confined to the decidua, the inner third of the myometrium, and the associated spiral arterioles. Extravillous cytotrophoblast cells give rise to interstitial cytotrophoblasts, which invade the stroma of the decidua and parts of the myometrium, and to endovascular cytotrophoblasts that migrate and invade along the wall of the uterine spiral arterioles. The consequence of these processes is the remodelling of the uterine spiral arterioles to provide low resistance, high flow blood vessels, allowing increased blood flow to the placenta to cope with the increasing nutritional demands of the rapidly growing fetus [9]. Thus, differentiation of cytotrophoblast cells is fundamental to normal human placental development. In particular, modification of the maternal vessels by extravillous cytotrophoblasts, which replace the maternal endothelium, is thought to be critical for the successful progression of pregnancy, since reduced invasion of interstitial and endovascular cytotrophoblasts is associated with pre-eclampsia and fetal growth restriction [10,11]. Thus, it is evident that elucidation of the key molecular mechanisms controlling trophoblast cell lineage commitment and identification of regulators of cytotrophoblast differentiation in humans is crucial for our understanding of normal and pathological placental development.

2. Transcriptional control of placental development

Growth factors and signalling molecules are the cues to which a cell responds, either by maintaining or altering its state of differentiation. However, it is the transcription factors that act within the cell nucleus which determine how these cues are interpreted

and what the cellular response will be. Transcription factors achieve this by regulating expression of their target genes within the cell. Numerous transcription factors play essential roles in cellular development and differentiation of a variety of cell types, including the trophoblast cell type in the placenta [5,12]. Transcription factors are categorised into a few large families such as the zinc finger, leucine zipper, helix-loop-helix, helix-turn-helix and homeobox genes [13,14] and also include the ligand-activated nuclear receptor superfamily. Our interest is in one of the largest and most important groups of transcription factors called the superfamily of homeobox genes. Several homeobox genes potentially control commitment and differentiation and were identified in human invasive extravillous cytotrophoblasts [15,16]. Our present knowledge of homeobox transcription factors that are involved in human feto-placental growth is summarised below.

3. Homeobox genes

Homeobox genes (also known as homeotic genes) were originally discovered in the fruit fly *Drosophila melanogaster*, where they act as transcriptional regulators to control embryonic development [reviewed in 17-19]. Homeobox genes contain a highly conserved 183 base pair homeobox sequence, which encodes a 61 amino acid motif called the homeodomain. Structural analyses reveal that the homeodomain consists of an evolutionarily conserved helix-turn-helix motif that binds to DNA. The specificity of this binding allows homeodomain proteins to activate or repress the expression of batteries of down-stream target genes [20]. Homeobox genes are subdivided into the “clustered” homeobox genes known as “HOX” genes, the “non-clustered” divergent or orphan HOX-like genes, as well as several distinct classes of atypical homeodomain containing genes. Homeobox genes are grouped together into subfamilies based on criteria such as their functional and structural characteristics. These subfamilies of homeobox genes are essential for the control of specific aspects of placental growth and differentiation [3, 12, 21].

Homeobox genes are directly or indirectly involved in a variety of developmental disorders, diseases and cancers [reviewed in 22]. Deregulation of specific homeobox genes in cancer and other diseases provides support for the idea that homeobox genes are crucial for normal mammalian development. Furthermore, characterisation of homeobox genes involved in disease progression may lead to a greater understanding of the developmental mechanisms that are disrupted in a variety of disease states. Normal homeobox gene expression is altered in various disease states. For example, decreased expression of Cdx2 is detected in the intestinal epithelium of patients with colorectal cancers and decreased Meox2 expression is detected in brain endothelial cells of patients affected by Alzheimer’s disease [22,23]. Thus, homeobox genes could be used as disease markers or potential therapeutic targets of diseases, such as cancer, diabetic wound healing, lymphedema, Alzheimer’s disease, and stroke due to atherosclerosis [24-26].

4. Homeobox genes in human feto-placental development

Several homeobox genes affect placental and embryonic development. Murine knockout models provide genetic proof that homeobox genes play a pivotal role in murine placental development. For example, targeted disruption of *Dlx3*, *Esx1* and *Tgif-1* murine homeobox genes result in placental maldevelopment and growth restricted phenotypes in embryos [27-29]. Therefore, understanding the expression and localisation of homeobox genes in human placental development and their role in pregnancy pathologies including fetal growth restriction (FGR) is highly important.

Our approach to understanding the molecular pathways of homeobox genes and their role in fetoplacental growth was based on the following strategy: (i) identifying the spatio-temporal expression pattern of homeobox genes in human placental development that have been identified as regulators of cell fate decisions during embryonic development; (ii) determining whether specific homeobox gene expression levels are altered in placentae from FGR-affected pregnancies compared to placentae from gestation-matched uncomplicated pregnancies; (iii) creating in vitro models using manipulated placental cultured cells that “mimic” homeobox gene expression changes detected in FGR placentae (the manipulation involves the use of loss- or gain-of-function phenotypes by RNA interference systems or gene overexpression plasmids); (iv) identifying the targets of homeobox genes using in vitro cell culture models; and (v) identifying hormonal regulators of homeobox genes. Similar strategies have been proven successful in identifying transcriptional control of endocrine functions during murine placental development [reviewed in 3]. Therefore, identification of the homeobox target genes, their targets and hormonal regulators in specialised cell types of the human placenta could reveal important molecular pathways responsible for fetoplacental growth. Using the strategy described above, we undertook extensive analyses of homeobox genes in placentae from FGR-affected and uncomplicated, gestation-matched control pregnancies.

5. Homeobox genes in the human placenta

5.1. Spatio-temporal expression patterns of homeobox genes in the placenta

We and others have identified the potential importance of homeobox genes *DLX3*, *DLX4*, *GAX*, *ESX1L*, *HLX* and *TGIF-1* in the human placenta [27, 30-34]. These homeobox genes are also expressed in the embryo and play pivotal roles in embryonic development [29, 35, 36]. More specifically, we demonstrated that homeobox gene *HLX* is expressed primarily in proliferating cytotrophoblast cell types during early placental development [32]. We also determined the expression profile of homeobox gene *DLX3* and *TGIF-1* in the human placenta [33, 34]. In first trimester and term placentae, *DLX3* and *TGIF-1* localised to the nuclei of villous cytotrophoblast cells, the syncytiotrophoblast layer and proliferating extravillous trophoblast cells in the proximal region of the invading cell columns. The following section summarises our current knowledge of homeobox gene regulation in human fetoplacental development, specifically in human trophoblast cells and reveals novel mechanisms behind trophoblast dysfunction, which is observed in placentae from FGR pregnancies.

5.2. Homeobox gene expression levels are changed in idiopathic FGR placentae compared with gestation-matched controls

The pattern of normal human fetal growth is complex. Evidence reveals that maximal growth rate for length is detected in the second trimester, whereas the maximal rate of weight gain is detected early in the third trimester [37-39]. Using a clinically well-defined cohort of FGR pregnancies, we identified homeobox genes that showed differential gene expression in FGR-affected placentae compared with gestation-matched control placentae. The cohort of FGR-affected pregnancies used for our studies was carefully defined in clinical terms, representing the severe end of the spectrum for idiopathic FGR. Idiopathic FGR pregnancies were identified with the general inclusion criterion of a birth weight less than the 10th centile for gestation age, employing Australian growth charts. FGR cases were classified as idiopathic if there was also evidence of underlying pathology, assessed by the presence of at least two of the following antenatal ultrasound diagnostic criteria: abnormal umbilical artery Doppler flow velocimetry, oligohydramnios [as determined by amniotic fluid index (AFI) <7], or asymmetric growth of the fetus as measured from the HC (head circumference) to AC (abdominal circumference) ratio (>1.2). Homeobox genes *HLX* [40] and *ESX1L* [41] showed reduced expression in idiopathic FGR-

affected placentae compared with gestation-matched placental controls. However, homeobox genes *DLX3*, *DLX4* and *TGIF-1* showed increased expression [34, 42, 43] in idiopathic FGR-affected placentae compared with gestation-matched controls. Our observation of altered homeobox gene expression levels, *i.e.* decreased (*HLX*, *ESX1L*) or increased (*DLX3*, *DLX4* and *TGIF-1*) expression in FGR-placentae compared with gestation matched controls, led us to model these effects in cell culture.

5.3. Creating *in vitro* models of placental cultured cells to “mimic” homeobox gene expression changes observed on FGR

Changes in the rate of trophoblast differentiation, proliferation and invasion are detected in FGR. We used well characterised, transformed, trophoblast-derived cell lines, which model first trimester human villous and extravillous cytotrophoblast cells, and which exhibit fundamental trophoblast cell properties including proliferation, differentiation, migration and invasion. The functional role of homeobox genes was determined by changing homeobox gene expression to “mimic” the changes observed in FGR. We used the techniques of gene inactivation or over-expression in these trophoblast-derived cell lines *in vitro*. For example, to assess the functional role of decreased *HLX* levels observed in FGR, we decreased *HLX* expression levels in trophoblast-derived cell lines SGHPL4 and HTR8-SV/neo using short-interference RNAs (siRNA) specific for *HLX* [44,45]. The functional role of *DLX3*, which showed increased expression in FGR, was determined by increasing the expression of *DLX3* in trophoblast-derived cell line, BeWo, using a *DLX3* over-expressing plasmid construct [46]. Over-expression of *DLX3* in BeWo cells augmented BeWo cell differentiation, as measured by the following differentiation markers: 3 β -HSD, syncytin and β -hCG protein. The complementary result of reduced BeWo cell differentiation was obtained when *DLX3* expression was reduced by the action of *DLX3* siRNA [47]. The above studies led us to conclude that homeobox genes may have several potentially important roles in the regulation of important functions of trophoblast cells during human placental development, including proliferation and differentiation.

5.4. Identification of downstream target genes of homeobox genes

Few studies of target genes regulated by transcription factors in the human placenta have been reported. Therefore, we attempted to identify the downstream targets of human placental homeobox genes by employing *in vitro* models of trophoblast-derived cell lines, which model villous and extravillous trophoblasts. We mimicked changes in expression of homeobox genes observed in FGR-affected placentae, either by gene inactivation or gene overexpression, and then determined which target genes were affected by these changes. For example, we used siRNA to inactivate *HLX* in SGHPL-4 and HTR-8/SVneo trophoblast cell line models and observed changes in gene expression levels for the MAP (mitogen activated signaling)- kinase signaling pathways. The downstream target genes of *HLX* were determined to be *RB1*, *MYC*, *EGR1*, *CDKN1C*, *ELK1*, *CCNB1* and *JUN* [45]. *HLX* homeobox gene targets were cell cycle regulatory genes in trophoblasts. Furthermore, our results provided evidence that decreased levels of *HLX* detected in FGR cause direct or indirect effects on cell-cycle regulatory genes and these target genes were also altered in FGR [45]. On the other hand, inactivation of homeobox gene *DLX3* in the trophoblast derived BeWo cell line, and in primary villous cytotrophoblasts, resulted in reduced expression of differentiation markers 3 β HSD, β hCG and syncytin [33]. Expression of 3 β HSD, β hCG, syncytin and *DLX3* was increased in FGR-affected placental tissues compared with controls, providing evidence that these genes are targets of *DLX3* [46]. Together, these data suggest homeobox genes have multiple potentially important roles in the regulation of trophoblast function during human placental development. Furthermore, there may be significant deleterious consequences to increased *DLX3* in FGR, through the action of target genes, 3 β HSD, β hCG and syncytin, on trophoblast function. Recent studies from our laboratory have identified the

transcription factors, peroxisome proliferator-activated receptors (PPAR) and GATA2 as additional candidate downstream target genes of *DLX3* [47]. This is potentially significant since PPAR γ and GATA2 are important genes in placental trophoblast differentiation, and the expression of PPAR γ and GATA2 is significantly changed in human FGR.

5.5. Endocrine regulators of homeobox genes

Our studies have thus far provided evidence that homeobox genes play a key role in cell-fate decisions during fetoplacental growth. However, little is known about the factors that control homeobox gene expression in the human placenta. Recently, members of the nuclear receptor superfamily and their cognate ligands were shown to regulate homeobox gene expression in both embryonic and adult tissues [reviewed in 47]. Endocrine control of homeobox genes during embryogenesis determines the axial expression of various homeobox genes that are necessary for body axis formation. For example, retinoic acid directly regulates *HOXB1* expression in the rostral embryonic domains where they are necessary for central nervous system development [48, 49]; estrogen is necessary for *HOXA9-11* expression, where it is important for caudal differentiation [50]; and the secosteroid hormone, vitamin D, regulates *HOXA10* expression during hematopoietic development [51].

Many adult organ systems, including the female reproductive tract and the hematopoietic system, retain developmental plasticity and there is ongoing tissue regeneration involving proliferation and differentiation, followed by degeneration. These organ systems are targets of endocrine control. The control processes in many ways recapitulate embryogenesis, therefore, it is not surprising that homeobox gene-mediated developmental programs driven by hormones are essential in these adult tissues and cells. For example, estrogens [52] and vitamin D [53], which are important in embryogenesis, are also active in adult tissues and provide functional differentiation of cells and tissues [47].

Placental hormones and their control of cell function during fetoplacental growth is well documented (reviewed in [54, 55]). Therefore, it is plausible that changes in endocrine regulation can result in dysregulated homeobox gene expression affecting placental development and function. In a recent study from our laboratory, we hypothesised that endocrine control of homeobox gene expression is necessary for diverse functions including proliferation, migration, invasion and differentiation of cytotrophoblasts of the human placenta. We have evidence to show that progesterone receptor (PGR) expression is significantly decreased in idiopathic FGR-affected placentae compared with gestation-matched controls [0.53 ± 0.09 , FGR (n=25) vs. 1.10 ± 0.31 , GMC (n=25), t-test, $p < 0.05$]. Immunoblotting revealed significantly reduced PGR protein (86 kDa) in FGR compared with GMC (Murthi et al., unpublished data). We also have evidence to show that PGR expression in trophoblasts influences placental cell homeobox gene expression. Using siRNA specific for PGR, we have identified that PGR expression is necessary for the expression of homeobox genes *HOXB2* and *HOXD12* that are known regulators of cellular proliferation. Furthermore, PGR inactivation increased the expression of homeobox genes *DLX3*, *HOXA10*, *HOXB9*, *TGIF-1*, *TLX2* and *PROX1*, which are regulators of cellular differentiation (Stevenson et al., unpublished data).

Recent studies in our laboratory have also identified that vitamin D receptor (VDR) expression is decreased in idiopathic FGR compared with controls (0.18 ± 0.04 , FGR (n=25) vs. 1.79 ± 0.35 , Control (n=25), $p < 0.05$). We have also recently demonstrated that

VDR inactivation in trophoblasts may contribute to reduced fetoplacental growth by modulating the expression of homeobox genes in trophoblasts *in vitro* (Cholangi et al., unpublished data). Our results provide evidence that VDR is necessary for the expression of homeobox genes *ARX*, *CDX-2*, *HLX*, *HOXB4*, *HOXC9*, *HOXD12*, *DLX2*, *DLX3*, *ESX-1*, *MEIS-2*, *NKX-3.1*, *TGIF-1*, *TLX2* and *VAX2* (Murthi et al., unpublished data). As depicted in Figure 1, growth factor, cytokines and pregnancy hormone-mediated signals in the human placenta may control fetoplacental growth by utilising the evolutionarily conserved homeobox gene-mediated developmental programs, which allows generation of structural and functional diversity in the human placenta and differential expression and functions of homeobox genes may contribute to reduced fetoplacental growth in human idiopathic FGR. Therefore, we propose that further elucidation of signaling pathways underlying the hormone-mediated homeobox gene developmental programs may offer novel strategies of targeted therapy for improving fetoplacental growth in idiopathic FGR pregnancies.

6. Conclusion

In this review, we have discussed the well-characterized roles of the homeobox genes in human placental development and function. Here, we also propose that a differential response to fluctuating hormone signals may form a key controlling mechanism for homeobox gene expression in the human placenta. By selectively modulating the activity of specific endocrine target genes, specific therapeutic effects for the clinical management of FGR can be achieved.

Conflict of interest statement

There is no conflict of interest. The author has nothing to disclose.

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Figure Legend

Figure 1 depicts how the regulation of homeobox gene expression by growth factors, pregnancy hormones and cytokines controls basic cellular functions such as proliferation, migration, invasion, differentiation and apoptosis of placental cells. In fetal growth restriction-affected pregnancies, differential expression and functions of homeobox genes may contribute to reduced fetoplacental growth.

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Figure 1

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