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REVIEW

Intrauterine growth restriction and genetic determinants - existing findings, problems, and further direction

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Abstract

Fetal growth is determined largely by the nutrient supply, placental transport function, and growth hormones. Recently, gene mutation and expression, especially of those genes associated with the proteins that are related to the fetal growth, have been reported to play an important role in the development of intrauterine growth restriction (IUGR). Fetal growth epigenetics, a new concept in fetal growth, has resulted from studies on fetal programing. This paper outlines the findings of our serial studies on IUGR, and summarizes data on IUGR animal models, placental function in transferring nutrients, cell proliferation dynamics in IUGR, and experimental treatment of IUGR. We review genetic approaches to IUGR, especially those relating to growth factor genes, angiotensinogen genes and other gene mutations. We also discuss the epigenetics of fetal growth and future study directions on fetal growth restriction. These should be valuable in elucidating the mechanisms employed by the fetus and in helping to develop interventional strategies that might prevent the development of IUGR.

Key words: Intrauterine growth restriction; Gene; Epigenetics; Placenta

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INTRODUCTION

Intrauterine growth restriction (IUGR) is an important obstetric complication affecting 5% of pregnancies[1]. This condition represents an *in utero* shift from the expected pattern of fetal growth potential into reduced birth weight. This leads to increased risk for intrauterine compromise, stillbirth, preterm birth and adverse perinatal and long-term outcomes[2-5]. It is generally accepted that IUGR is associated with a poor nutrient and oxygen supply, although the specific mechanisms involved in IUGR development are mostly unknown.

Fetal growth is determined largely by the nutrient supply, which is dependent on placental transport functions. Though placental transportation depends on the concentration gradient between maternal and fetal blood, it seems that placental blood flow and the activity of specific membrane transporters play more important role[6,7]. Regardless of what the exact mechanism for IUGR might be, growth factors and their interaction with their receptors are most likely to be involved[8]. In addition to nutrition, placental function, and growth hormones, gene mutation and expression have been reported to be associated with IUGR[9-13]. Those genes associated with the proteins that are related to the fetal growth such as growth factor genes are particularly implicated. In recent years, a

new concept in fetal growth, fetal growth epigenetics, has resulted from studies on fetal programing[3,14-16].

The information in this paper outlines findings from our serial studies on IUGR and reviews the genetic approaches in recent years. This should be valuable in the elucidation of the mechanisms employed by the fetus and help in the development of interventional strategies that might prevent the development of IUGR.

EXISTING FINDINGS

IUGR animal models

Several methods have been used to establish the animal model of IUGR. These include uterine artery ligation, passive smoking, alcohol exposure, administration of L-arginine or actinomycin, and maternal malnutrition. To date, mouse, rat, guinea pig, rabbit, sheep, monkey, dog, and pig have been used to establish the IUGR model[17-19].

We have reported the establishment of an IUGR rabbit model using passive smoking and have studied the fetal and maternal plasma amino acid concentration, the blood flow of utero-placenta and changes in cell proliferation cycle in brain, liver and placenta[20,21]. In addition, the effect of treatment with histiocyte activators and vasodilators on the IUGR was also observed[7,18]. Recent studies on gene mutations have shown that specific genes might play an important role in the development of IUGR[9-16].

Active transfer of nutrients through the placenta

Although fetal plasma nutrient concentration is related to the maternal concentration, some amino acids, especially most essential amino acids, show higher concentrations in fetal plasma than in maternal plasma, proving that the absorption of amino acids from the maternal body to the fetus is an active process[22]. Maternal rabbit total plasma amino acid concentration at 28-d of pregnancy was less than that of non-pregnant rabbits. These changes were more apparent with essential amino acids. In the rabbit IUGR model, smoking could reduce the ability of the placenta to transfer nutrients from the maternal to the fetal side. It was found that the total amino acid concentration in fetus was lower in rabbits with IUGR induced by smoking than in controls. In fetal plasma, the levels of all essential amino acids, except threonine, and of nonessential amino acids including serine, glutamine, alanine, tyrosine, arginine and histidine showed the same patterns in smoking groups as in the control group[7,20].

Dynamics of cell proliferation in IUGR

Cell proliferation in the fetus is very active, especially in early embryo phase. Proliferation depends on the cell division, as measured by analyzing the cell cycle using flow cytometry. The more rapid the cell division, the shorter the G_0 and G_1 phases. In another words, lower proliferation will leave more cells in G_0 or G_1 phase, while active proliferation will result in more in S + G_2 + M phases. By analyzing the cell cycle using flow cytometry, we found that the ratio of the cells in G_0 + G_1 phases to the total cells was increased and the ratio of the cells in S + G_2 + M phases to the total cells was decreased in fetal brain, liver and placenta in IUGR rabbits induced by passive smoking. This change was particularly prominent in brain. These results suggest that the proliferation of the fetal cells and placenta were inhibited significantly, resulting in growth retardation of the fetus. This data demonstrated that the transformation from G_1 to S phases was restricted in IUGR and that cell proliferation is prevented[21,23].

Experimental treatment of IUGR

IUGR rabbits caused by passive smoking were treated with histiocyte activators (include ATP, Co-A, and Cyt-C) and vasodilators (InjectioSalviaeMoltiorrhizaeComposita). The results showed that the vasodilators could increase the uteroplacental blood flow by about 35% and induced some progress in fetal development, as indicated by a 9.8% increase in fetal body weight. The fetal plasma amino acid concentration was also higher than that of the control group. It seems that the histiocyte activators were more effective in promoting fetal development (24.6% increase of fetal body weight) than the vasodilators. Although the effect of the histiocyte activators was not as marked as that of vasodilators in increasing uteroplacental blood flow, the amino acid concentration of fetal plasma increased more after histiocyte activator treatment than vasodilator treatment. This suggests that vasodilators could be used to treat the IUGR caused by vasospasm. Histiocyte activators appear to be better than vasodilators in increasing the nutrient transportation of the placenta[24].

IUGR AND GENE APPROACHES

Although the human genome contains about 30 000 genes only a small number of them are turned on within a particular tissue type. Cell proliferation and differentiation results from the ability of tissues to express different genes from the same basic set of genetic information stored in DNA. This small subset of genes allows the cells to produce proteins unique to their functions. Although gene expression is controlled by epigenetic modifications, the gene sequence obviously plays the most important role in the proliferation and differentiation of cells.

IUGR and growth factor genes

Several studies have demonstrated altered concentrations of human placental growth hormones (hPGH), insulin-like growth factor-I (IGF-I) and IGF banding protein (IGFBPs) in the maternal circulation and the fetal compartment in pregnancies with IUGR[25,26]. Koutsaki, evaluating the expression status of the *hPGH*, the *IGF-I*, *IGFBP-1* and *IGFBP-3* genes in placentas from human IUGR pregnancies of no apparent etiology, found that *hPGH*, *IGF-I*, *IGFBP-1* and *IGFBP-3* expression was significantly lower than that in placentas showing normal

fetal growth. However, these alterations are not known causative factors of IUGR or associated with other pathogenetic mechanisms[27].

Type I insulin-like growth factor receptor (*IGF-IR*) is widely expressed across many cell types in fetal and postnatal tissues. The activation of this receptor, after the binding of secreted *IGF-I* and *IGF-IR* promotes cell differentiation and proliferation. An association has been found between IGF-*IR* gene mutations and low birth weight[28]. *IGF-IR* gene anomalies such as heterozygous *IGF-IR* mutation or insufficiency of the *IGF-IR* gene were found in patients presenting with low birth weight and birth height[29,30]. This phenotype is associated with family history of low birth weight and a normal or increased *IGF-I* level and/or a normal or increased GH response to GH stimulation test[31,32]. However, such patients show less response to GH treatment than common small for gestational age short-stature patients[33].

Choi *et al*[34] reported a family with both a novel heterozygous mutation of the *IGF-1R* gene and a segmental deletion encompassing the entire *IGF-1R*, resulting in *IGF-I* resistance and leading to IUGR and postnatal growth failure. *In vitro* studies of fibroblasts from subjects carrying the gene clearly demonstrated reduced *IGF-1R* expression and subsequent *IGF-I* resistance, as assessed by *IGF-1R* phosphorylation and post-receptor signal transduction. This indicates that *IGF-1R* mutations should be considered in the differential diagnosis of familial IUGR patients with persistent short stature[34]. Umbers found that material inflammation of the placenta could disturb the *IGF* expression and cause IUGR[35].

Experiments in animals demonstrated the importance of *IGF* in the regulation of both intrauterine and postnatal growth. Baker reported that isolated inactivation of *IGF-I* resulted in restrictions in fetal development (40% delay compared with wild type mice) and Liu found that postnatal growth was further impaired, reaching only 30% of that in normal mice[36,37]. Knockout of both *IGF-I* and *IGF-II* or knockout of both *IGF-II* and *IGF-I* receptors resulted in severe growth retardation (Figure 1)[38]. These experiments clearly demonstrated that *IGF-I* is a major regulator of both pre- and postnatal growth. Several authors reporting *IGF-IR* gene mutations observed effects on birth weight, height, serum *IGF-I* and additional complications (Table 1).

Table 1 *IGF-I* receptor mutations

Gene mutation	Birth weight (SD)	Birth height (SD)	Complications
Arg108Gln/ Lys115Asn	-3.5	-4.8	Microcephaly, abnormal speech[29]
Arg59Ter	-3.5	-3.0	Microcephaly, Delay in speech[29]
Arg709Gln	-1.5	-2.6	Mental retardation[28]
Gly1050Lys	-2.1	-4.0	Insulin resistance[32]
Arg281Gln	-3.1	-5.0	Decreased cell proliferation[31]
Val599Glu	-2.3	-2.1	Developmental delay[33]
Gly1125Ala	-1.8	-3.6	Microcephaly, clinodactyly, delayed menarche, diabetes mellitus[30]

Table 2 Maternal AGT Thr235 genotypes[40]

Groups	No.	Genotype			*P* value
		MM (%)	MT (%)	TT (%)	
Control	400	170 (42.5)	158 (39.5)	72 (18.0)	
IUGR	174	33 (19.0)	66 (37.9)	75 (43.1)	< 0.001
Preeclampsia + IUGR	60	11 (18.3)	24 (40.0)	25 (41.7)	< 0.001
Placental abruption	62	9 (14.5)	27 (43.5)	26 (41.9)	< 0.001

IUGR: Intrauterine growth restriction.

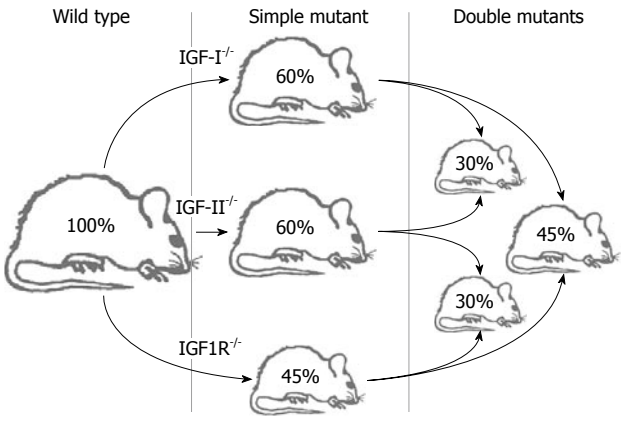

Figure 1 Effects of disruption of the insulin-like growth factor system on fetal growth in mice, expressed as a percentage of normal body weight[38]. IGF: Insulin-like growth factor.

IUGR and angiotensinogen gene

IUGR has been associated with insufficient placental circulation, which may result from failed maternal physiologic changes such as abnormal spiral artery remodeling and reduced maternal blood volume. Morgan reported that spiral artery remodeling might be related to the angiotensinogen gene[39]. We compared maternal blood DNA in 174 patients with IUGR, 62 patients with placental abruption, and 60 patients with both preeclampsia compared with a control group comprising 400 consecutive cases of women with term pregnancies and infants with birth weight between the 5th and 95th percentiles. We also examined 162 DNA samples from fetal blood with IUGR and 240 normal fetuses from control group for the Thr235 polymorphism[40] (Tables 2 and 3).

According to the AGT genotyping results using real time PCR, angiotensinogen genotypes were divided into three groups: MM (homozygous for angiotensinogen Met235 allele), TT (homozygous for angiotensinogen Thr235 allele), and MT (heterozygous). It has been demonstrated that maternal and fetal angiotensinogen Thr235 genotypes are associated with an increased risk of IUGR[40]. The angiotensinogen Thr235 allele may

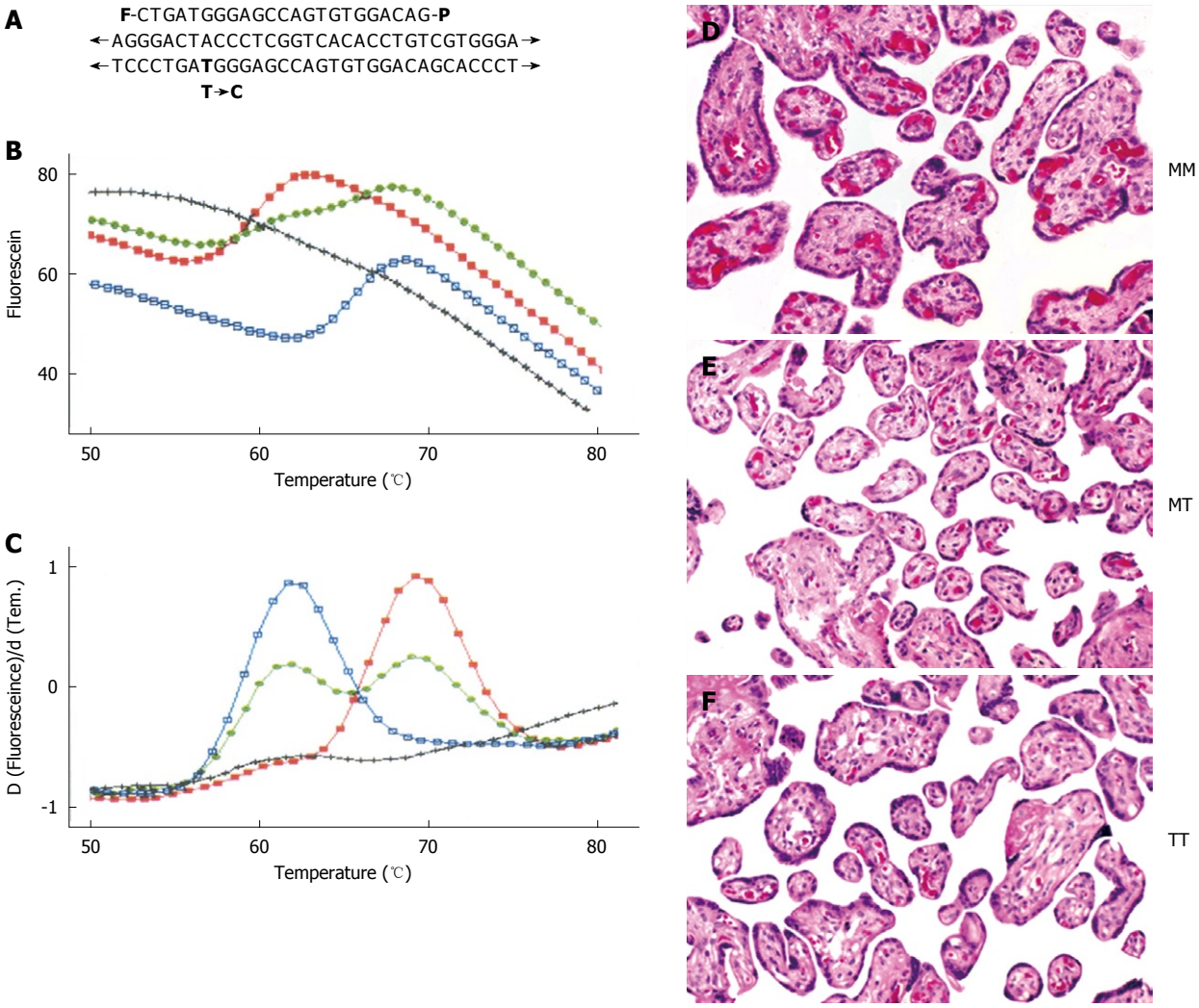

Figure 2 Real-time polymerase chain reaction for angiotensinogen M235T genotyping with a single labeled fluorescein probe[42]. A: 5'-fluorescein-labeled 23-mer (blocked at the 3'-end with phosphate) homologous to the wild-type sequence, covered the polymorphic site with the fluorescein opposite two genes; B: The probe was included in the PCR amplification mixture with primers. Melting curve data are presented as fluorescein *vs* temperature; C: Curves for homozygous wild type (peak at 69.4oC), homozygous mutant type (peak at 63.54oC), heterozygous (two peaks at 63.54oC and 69.44oC respectively) and no-template control are shown; D: Placental cross section HE staining from AGT MM, MT, and TT placentas. Quantitative analysis of the placenta indicated that the villus area (red) and capillary area (bright red) in smoking-induced intrauterine growth restriction were significantly decreased.

Table 3 AGT Thr235 alleles frequencies analysis[40]

Groups	AGT genotype		T Allele Freq.	*P* value
	Met235 alleles	Thr235 alleles		
Maternal DNA				
Control (400)	498	302	0.378	
IUGR (174)	140	208	0.598	< 0.001
Preeclampsia + IUGR (60)	44	76	0.633	< 0.001
Placental abruption (62)	45	79	0.637	< 0.001
Fetal DNA				
Control (240)	298	182	0.379	
IUGR (160)	131	189	0.591	< 0.001

IUGR: Intrauterine growth restriction.

predispose women to deliver growth-restricted fetuses. Further studies have shown that mutation of angiotensinogen gene Thr235 is also a risk factor for preeclampsia and placental abruption[41] (Table 2). In addition, quantitative analysis of the placenta indicated that the villus area was decreased significantly in the IUGR group induced by smoking exposure. The capillary area in the villus was also significantly less in IUGR groups. There were also some important changes observed under the electronic microscope, such as the retardation and reduced number of microvilli, fatty degeneration and mitochondrial swelling of the syncytial cells[42]. Studies on human placenta showed that villus volume and capillary area in IUGR were significantly decreased (Figure 2 and Table 4).

Other gene mutations

It has been reported in many publications that certain gene mutations are associated with IUGR (Table 3). Pericentric inversion of chromosome 6 causes haploinsufficiency of the *CDK19* gene resulting in microcephaly, congenital bilateral falciform retinal folds, nys-

Table 4 AGT genotype and placental findings[42]

AGT genotype	MM	MT	TT
No. of placentas	8	13	14
Clinical findings			
Maternal age (yr)	26.0 ± 4.7	26.6 ± 6.6	29.8 ± 6.5
Gestational age (wk)	36.2 ± 4.5	36.6 ± 1.9	36.7 ± 3.1
Fetal birth wt. (g)	2730 ± 967	2642 ± 541	2620 ± 535
Placental quantitative findings:			
Number of villi (mm^2)	155.3 ± 14.1	145.8 ± 28.0	146.3 ± 27.7
Villous CS area (μm^2/villous)	4422.2 ± 550.0	4400.9 ± 813.5	4248.6 ± 1191.9
Villous volume/1 cm^3 placenta (cm^3)	0.668 ± 0.034	0.626 ± 0.022[b]	0.587 ± 0.059[b,c]
Capillary volume/1 cm^3 placenta (cm^3)	0.131 ± 0.029	0.107 ± 0.034	0.070 ± 0.030[b]
Intervillous volume/1 cm^3 placenta (cm^3)	0.332 ± 0.034	0.374 ± 0.022[b]	0.413 ± 0.059[b,c]
Placental quantitative analysis:			
Volume of trimmed placenta (cm^3)	324.8 ± 128.0	355.2 ± 80.3	374.1 ± 70.2
Villous total volume per placenta (cm^3)	215.8 ± 81.8	222.1 ± 50.7	219.9 ± 52.6
Intervillous space per placenta (cm^3)	108.9 ± 47.8	133.1 ± 31.1	154.2 ± 38.6[a]
Villous capillary volume per placenta (cm^3)	45.1 ± 27.4	41.4 ± 23.2	26.6 ± 14.4[a]
Percentage of villous capillary volume (%)	19.81 ± 5.12	17.41 ± 7.3	12.06 ± 5.45[a]
Villous surface area per placenta (m^2)	9.029 ± 3.285	9.560 ± 2.031	10.370 ± 2.725
Villous surface per 1 g plac. Villi (cm^2)	390.6 ± 35.0	401.6 ± 40.5	438.6 ± 73.8

[a]$P < 0.05$, [b]$P < 0.01$ *vs* MM; [c]$P < 0.05$ *vs* MT.

tagmus, and mental retardation[9]. Chromosome 1p32-p31-deletion syndrome and haplo-insufficiency of the *NFIA* gene may present as ventriculomegaly, corpus callosum hypogenesis, abnormal external genitalia, and IUGR in the third trimester[10]. Smigiel reported on two brothers affected with restrictive dermopathy, who died in the neonatal period[43]. Molecular analyses were performed in the second child, for whom biological material was available, and on both parents. Compound heterozygous frameshifting mutations were identified in exon 1 (c.50delA) and exon 5 (c.584_585delAT) of the *ZMPSTE24* gene. The autosomal recessive inheritance was confirmed by genomic analysis of the parents. Partial loss of Ascl2 function affects all three layers of the mature placenta and causes IUGR[44]. The expression of *c-fos* is critical in the oxidative stress pathway. In fetal alcohol syndrome in mouse, it was shown that alcohol administration during pregnancy results in differential gene expression in the stress signal pathway, particularly in *c-fos*. *C-fos* expression in the decidua increases from 6 to 24 h after alcohol injection, but does not change in the embryo, which may contribute to alcohol-induced damage in fetal alcohol syndrome (Table 5)[45].

Epigenetics of fetal growth

Mechanisms leading to the attenuation of fetal birth weight and adverse pregnancy outcomes are complex. Many studies have begun to focus, not only on the contribution of maternal and fetal genes to phenotypic outcome, but also on epigenetic changes associated with fetal growth[46].

Imprinted genes have a central role in the development and function of the placenta and have been implicated in a variety of disorders affecting fetal growth[14-16,47,48]. Gene inactivation studies in mice and chromosomal rearrangements in humans have demonstrated that many of these imprinted genes play key roles in placental development and function as well as in fetal growth. Those studies have also demonstrated that imprinted genes act in a complex manner at many levels to affect the energy balance between the mother and fetus. More recent studies also support a role of imprinted genes in a compensatory response to reduced fetal growth in humans.

During early embryonic development, the first stage of embryo differentiation establishes two cell lineages. These are the inner cell mass that forms all the tissues of the adult, and the trophectoderm that eventually produces placental structures. Generally speaking, the inner cell mass becomes gene hypermethylated and the trophectoderm becomes gene hypomethylated. These methylation patterns may be preserved throughout the whole pregnancy period[49,50]. Mouse and human models suggest the epigenetic regulation of fetal growth may also play a significant role through the placental imprinted genes.

Lambertini *et al*[48] investigated the differential methylation status of the imprinted genome to gain insights into the importance of the epigenetic regulation of these genes in fetal development by comparing IUGR with normal placentas. They found that differential methylation showed a highly significant correlation with gene length. The data also suggests that differential methylation changes in growth-restricted placentas occur throughout the genomic regions encompassing genes actively expressed in the placenta. Kumar studied 11 *IGF* related genes and found upregulated *ZNF127* gene expression and down regulated *PHLDA2* gene expression. This change confirmed an increased placental expression of growth-promoting imprinted genes and decreased expression of growth-suppressive imprinted genes with advancing gestational age. These changes in placental gene expression could potentially explain accelerated fetal growth seen in the third trimester[51]. McMinn presented

Table 5 Gene and fetal growth

Gene	Gene mutation/expression	Phneotypic effects/complications
CDK19	Chromosome breakpoints in 6p12.1 and 6q21	Microcephaly, congenital bilateral falciform retinal folds, nystagmus, and mental retardation[9]
NFIA	Chromosome 1p32-p31 deletion syndrome	Ventriculomegaly, corpus callosum hypogenesis, abnormal external genitalia, and intrauterine growth restriction in the third trimester[44]
IGF1R	Novel c.420del mutation in exon 2 of the *IGF1R* gene	Reduced *IGF1R* expression and represents haploinsufficiency of the *IGF1R* gene. IUGR and neonatal growth retardation[10]
hPGH, IGF-I, IGFBP-1	Decreased expression	Decreased expression is associated with IUGR[27]
c-fos	Decreased expression	Fetal alcohol syndrome[45]
11b-HSD2	Glucocorticoid metabolism	Under expression cause IUGR, small placenta[55]
GSTP1	Glutathione transferase enzymes pathway	Fetal growth and neonatal growth[56]
ZMPSTE24	Fetal growth	IUGR, dermopathy, neonatal death[43]
Ascl2	Placenta development	Three layers malformation, IUGR[44]
TFRC	Transferrin receptor function	IUGR[13]
DIO3	Type 3 deiodinase	Highly expressed in placenta and fetus. IUGR and hypothyroidism[47]
DLK1	Growth promoter	Expressed in placental villi. Methylation defects associated with IUGR[16]
HYMAI	Non-coding RNA	Transient neonatal diabetes and IUGR[57]
IGF2	Growth Factor	Placental and fetal growth restriction[58]
KCNQ1OT1	Non-coding RNA	Control placental Kcnq1 domain. Involved in Beckwith-Wiedemann syndrome[59]
MAGEL2/NDNL1	Similarity to NDN	Neonatal growth retardation, alter metabolism[60]
MEST	Neuronal differentiation	Fetal growth restriction, smaller placentas[52]
PEG10	Retrotransposon-derivedgene	Severe growth retardation, absence of spongiotrophoblast layer, embryonic lethality[61]
PEG3	Inhibits WNT-signalling	Placental and fetal growth restriction and abnormal maternal behavior[62]
PLAGL1 Zac1	Tumor suppressor	Skeletal defects, neonatal lethality, IUGR, and disrupted transactivation of Igf2[63]
SFRP2	WNT signaling	Reduction in vitro of extra villous trophoblast invasion[64]
HBII-85/PWScr	C/D Box small RNA	Implicated in Prader Willi, Postnatal growth retardation[65]

IUGR: Intrauterine growth restriction.

an excellent example of the complexity of the imprint gene in placenta[52]. He showed that a small group of imprinted genes (*PHLDA2*, *MEST*, *MEG3*, *GATM*, *GNAS* and *PLAGL1*) and an additional 400 genes were affected in IUGR placentas.

Many studies have reported changes in imprinted gene expression and methylation levels in response to IUGR. These include reports of abnormal methylation in multiple imprinted loci[16], IUGR placental methylation decrease in the IGF2/H19 locus[53], and differential expression in multiple imprinted genes in IUGR placentas[54].

PROBLEMS AND FUTURE DIRECTION

IUGR animal models and clinical IUGR

IUGR animal models have been established by several methods. Most of the methods affect nutrients, placental function, or maternal fetal circulation although some may affect gene expression. These IUGR models have provided valuable simulations allowing study human IUGR, especially the IUGR resulting from nutritional factors, placental function, or toxic materials. However, no animal IUGR model induced by gene mutation or altered gene expression, simulating human IUGR related to specific genes has been reported. To date, the development of gene engineering and transgenic techniques have made it possible to produce specific gene mutation/expression altered IUGR animal models. This kind of animal model will provide a direct and definite method to study the specific genes involved in IUGR.

Single gene study and many genes related to IUGR

A concern of the present studies is that only limited numbers of genes have been studied among the thousands genes that are expressed in placenta, while many genes are in fact associated with fetal growth. Evaluation of their important roles in fetal growth still requires the accumulation of multiple collections of data on the mutation, phenotype, epigenetics, and metabolomics associated with fetal growth characteristics. Specifically, the pathways involved in the mutation or epigenetics resulting in IUGR phenotype are mostly unknown. Basic study of the pathways involving these genes may help us to understand why and how the phenomenon occurs at the molecular level.

Role of genes in IUGR

Although it seems simple to define the diagnosis of IUGR as an estimated fetal weight falling below the 10th percentile of normal body weight, that definition also captures births that are part of the normal variation in a population. Clinical diagnostic criteria are based on the fetal growth curve and umbilical blood velocity abnormalities. However, IUGR is still an extremely complex phenotype to dissect because of the many factors involved, maternal, fetal, placental, and environmental. Al-

most all recent gene expression studies are based on small number of samples. It is unrealistic to expect to find one or a few genes responsible for causing IUGR using this approach. Most gene expression studies have found genes that are dysregulated in IUGR. In addition, most of these genes, such as *IGF-I*, *IGFBP1*, corticotropin-releasing hormone, are reported to be related to the regulation of cell division and proliferation. We are still unable to to determine whether this is a compensatory response to restricted fetal restricted growth or a the factors which induces fetal growth restriction. The use of transgenic engineering technique in animals to study some specific gene may provide an ideal model to study the phenotype related to these genes in human clinical subjects.

Gene promoting and IUGR

Some specific imprinted genes are related to IUGR. These genes can be separated into two categories: genes participating in reducing fetal growth, and those which increase fetal growth as a compensatory response when it is sensed that the fetus is at risk. The evidence supporting mutations in imprinted genes that negatively influence fetal growth is summarized in the table and genes which the positively influence fetal growth are also indicated. We may expect that reducing expression of the negative genes and increase the expression of the positive genes would result in fetal growth. However, there is still a long way to go from basic animal model studies to reach clinical applications using gene-regulating techniques.

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