Fetal growth and insulin-like growth factor system

Mitsutoshi Iwashita, MD

Department of Obstetrics and Gynecology, Kyorin University School of Medicine, Tokyo

Insulin-like growth factors (IGF-I and IGF-II) stimulate extravillous trophoblast (EVT) cells migration and invasion into uterine wall and one of IGF binding proteins (IGFBPs), IGFBP-1 inhibits IGF action thereby regulating EVT cells invasion negatively. Thus, appropriate placentation is determined by the balance of IGF and IGFBP-1 in maternal-fetal interface. IGF-I stimulates amino acids uptake by trophoblast cells in vitro and enhances the transfer of maternal amino acids to fetus in vivo. In contrast, IGFBP-1 inhibits IGF-I action in placenta in terms of maternal amino acids transfer to fetus. In mother, circulating levels of IGF-I are increased during pregnancy and correlate with birth weight while IGFBP-1 gradually increased throughout pregnancy and negatively correlates with birth weight. Thus, maternal IGF-I and IGFBP-1 are tightly involved in fetal growth presumably by regulating placental nutrient transfer to fetus. Fetal circulating levels of IGF-I are positively and IGFBP-1 are negatively correlate with birth weight as well. Cell culture and animal experiments clearly demonstrate that fetal IGF-I and IGFBP-1 are regulated by nutritional factors where fetus inhibits IGFBP-1 production under enough supply of nutrition from placenta and promotes its own growth. A condition that decreases supply of these substances such as placental dysfunction, fetus produces more IGFBP-1 and inhibits IGF-I action in order to inhibit own growth to survive. Although fetal circulating levels of IGF-I are much lower than those in mother, different profiles of phosphoisoforms of IGFBP-1 between mother and fetus may explain remarkable fetal growth due to high bioactivity of IGF-I in fetus.

Keywords: fetal growth, placenta, IGF, IGFBP-1, phosphoisoforms

A magzati növekedés és az inzulinszerű növekedési faktorrendszer

Az extravillosus trophoblast (EVT) sejtek migrációját és inváziójét a méhfalba az inzulinszerű növekedési faktorok (IGF-I és IGF-II) stimulálják. Az IGF-kötő fehérjék (IGFBP) közül az IGFBP-1 gátolja az IGF-aktivitást, tehát szabályozza, csökkenti az EVT-sejtek inváziójét. Az IGF és IGFBP-1 egyensúlya ezáltal elősegíti a szabályos placentációt az anyai–magzati határfelületen (foeto-maternális interface). Az IGF-I in vitro stimulálja az aminosav-felvételt a trophoblast sejtekbe, in vivo pedig segíti az aminosavak transzportját az anyából a magzatba. Az IGFBP-1 ezzel szemben gátolja az IGF-I hatását, tehát az anyai aminosavak placentán keresztül történő magzatba juttatását. Az anya szérum IGF-I szintje emelkedett a terhesség ideje alatt és pozitívan befolyásolja a születési súlyt, míg az IGFBP-1 szint fokozatosan emelkedik a terhesség során, és negatív összefüggést mutat a születési súllyal. Az anyai IGF-I és IGFBP-1 ezáltal kiemelkedő szerepet játszik a magzati növekedésben, feltehetően a tápanyagoknak a placentából a magzatba juttatásának szabályozásával. A magzati szérum IGF-I-szint növeli, míg az IGFBP-1-szint csökkenti a magzat születési súlyát. Sejtkultúrákban és állatkísérletekben egyértelműen kimutatható, hogy a magzati IGF-I- és IGFBP-1-szintet táplálkozási tényezők szabályozzák. Amennyiben elegendő tápanyag érkezik a placenta irányából, a magzatban az IGFBP-1-termelődés gátlódik, és így a magzat súlygyarapodása következik be. Tápanyaghiányos állapotokban, például placenta-diszfunkció esetén, a magzat több IGFBP-1-molekulát állít elő, és gátolja az IGF-I által közvetített súlygyarapodást saját túlélése érdekében. Annak ellenére, hogy a magzati szérum IGF-I-szint jóval alacsonyabb, mint az anyai, jelentős magzati súlygyarapodás következhet be; ez a kettejük eltérő IGFBP-1 foszfoizoforma profiljával magyarázható, és az IGF-I magas magzati bioaktivitásának köszönhető.

Kulcsszavak: magzati növekedés, méhlepény, IGF, IGFBP-1, foszfoizoforma

IGF system

Insulin-like growth factor (IGF) is one of growth factors that has insulin like activity. There are two similar peptides, namely IGF-I and IGF-II [1, 2] that are interacting with their receptors (type I and II receptors) on cell surface. Most of biological actions of IGF is believed to be mediated through type I IGF receptor (IGF-I receptor) that structure is similar to insulin receptor. Most IGFs are bound to specific binding proteins in biological fluids and at present six distinct IGF binding proteins are identified namely IGFBP-1, 2, 3, 4, 5 and 6 [3]. IGFBPs mostly inhibit but in some case enhance IGF action [4]. IGFBPs are proteolysed by specific proteases [5, 6] that indirectly modify IGF action *(Figure 1)*.

Correspondence:
Mitsutoshi Iwashita, Shinkawa 6-20-2, Mitaka City, Tokyo, JAPAN, iwashita@ks.kyorin-u.ac.jp

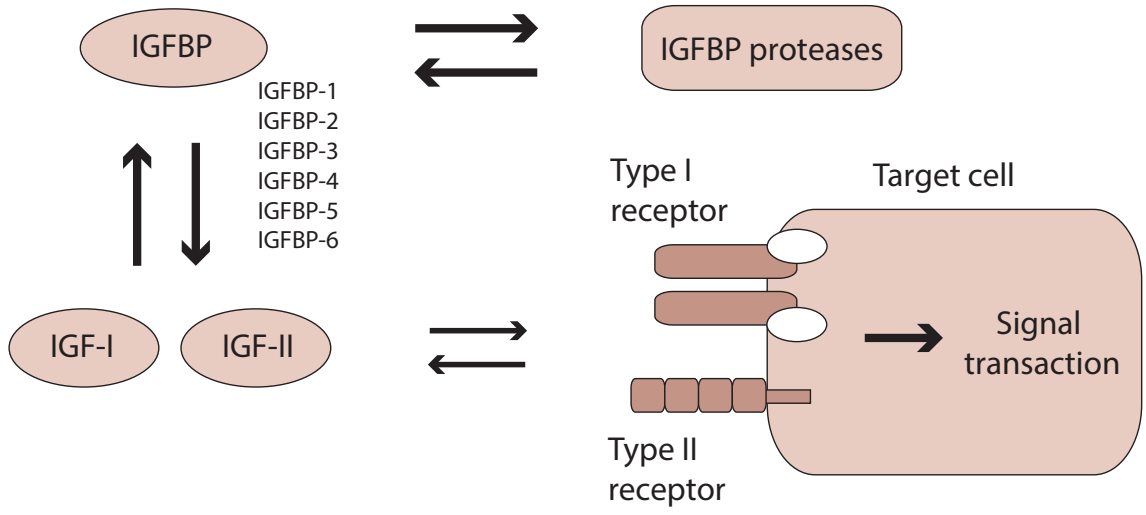

Figure 1. IGF system

IGF action in trophoblast cells

Implantation process consists of two cell biological events including attachment and invasion of trophoblast cells [7]. In invasion process, trophoblast cells migrate and proteolyse extracellular matrix of uterine endometrial cells. IGF-I treatment causes remarkable changes of cell shape in which extravillous trophoblast (EVT) cells extend lamelipodia and attach strongly on fibronectin coated culture dish *(Figure 2)* [8]. Attachment assay and migration assay clearly demonstrate that IGF-I stimulates extravillous trophoblast attachment and migration. In attachment assay, IGF-I stimulates EVT cells attachment dose dependently *(Figure 3 and 4)* [8] and IGFBP-1 inhibits IGF-I action. IGF-I induced attachment is abolished by the addition of alpha IR3, an IGF-I receptor antibody *(Figure 4)* suggesting that IGF-I stimulates cell attachment through IGF-I receptor.

In migration assay, EVT cells migrated through pores on the bottom of inner culture well are increased by IGF-I dose dependently [9] and this is inhibited by the addition of alpha IR3 with IGF-I suggesting that IGF-I stimulates trophoblast migration through its receptor as well *(Figure 5)*. IGF-I-stimulated cell migration was also blocked by IGFBP-1 *(Figure 5)*.

Placenta produces IGF-I and IGF-II and their receptors [10, 11] that stimulate trophoblast migration and proliferation in an autocrine fashion. In contrast, decidual cells produce large amounts of IGFBP-1 [12] that inhibits IGF action [13,

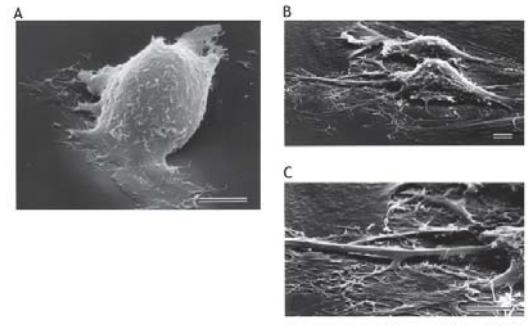

Figure 2. IGF-I-induced morphological changes in EVT cells (scanning electron microscopy)
Serum-starved EVT cells are seeded and treated for 2 hr with serum-free medium containing no addition (A) or 10 nM IGF-I (B and C). Scale bars, 10 µm.

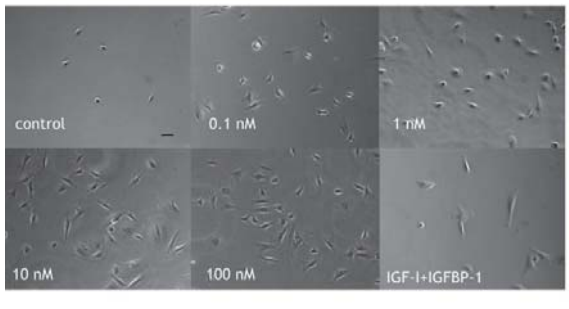

Figure 3. Effect of IGF-I on attachment of EVT cells
EVT cells are incubated in culture dish in the presence of IGF-I (0.1-100 nM) or 10 nM IGF-I + 10 nM IGFBP-1 for 1 hr. Then atteched cell number on dish is counted after several washes.

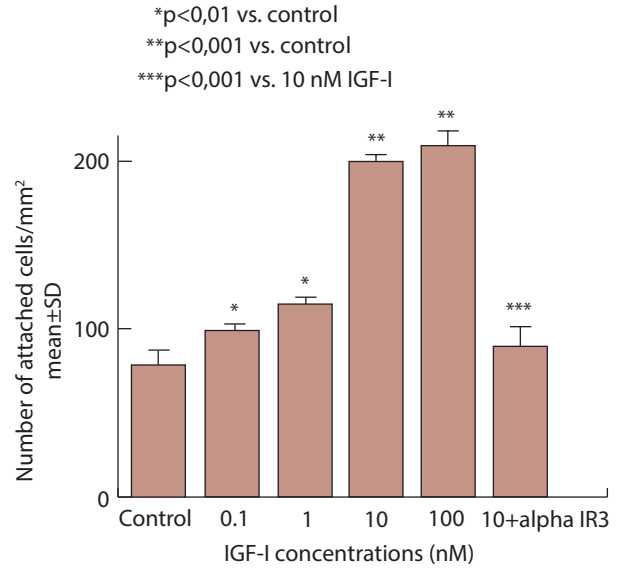

Figure 4. Attachment of EVT by IGF-I
EVT cells are incubated in culture dish in the presence of IGF-I (0.1-100 nM) or 10 nM IGF-I + 10 nM alpha IR3 for 1 hr. Then attached cell number on dish is counted after several washes.

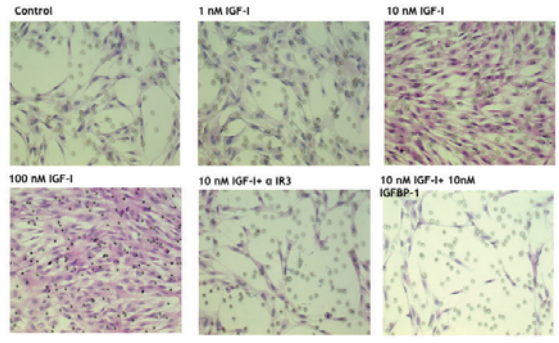

Figure 5. IGF-I-induced EVT cell migration
EVT cells are cultured in inner well of double chanber that has small pores on the bottom. Cells are incubated for 24 hr in the presence of indicated concentrations of IGF-I, 10 nM alpha IP3 or 10 nM IGFBP-1 in the presence of 10nM IGF-I and cells passed through pores are stained and counted

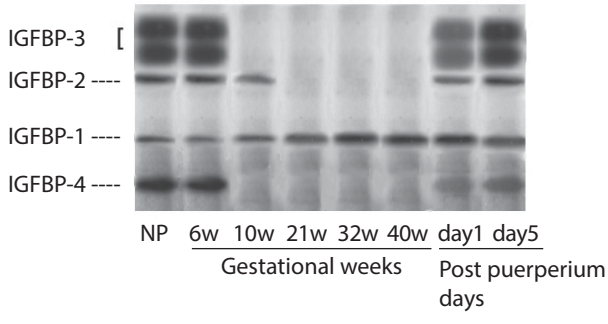

Figure 7. Western ligand blot of sera from nonpregnant (NP) women, pregnant women at various gestational weeks and post-puerperium

14]. Therefore, it is suggested that the balance of placental IGF and decidual IGFBP-1 production is important for controlled trophoblast invasion into uterine endometrium. If trophoblastic IGF production is exceeded than decidual IGFBP-1 production, trophoblast invades unlimitedly that is seen in tubal pregnancy, cervical pregnancy and placental increta and percreta. In contrast, over production of IGFBP-1

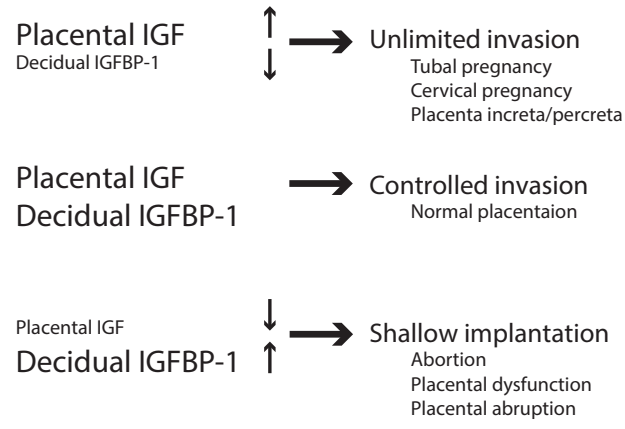

Figure 6. Imbalance of placental IGF and decidual IGFBP-1 production and abnormal pregnancy

in decidua compared to IGF production by placenta causes so called shallow implantation that is seen in abortion, placental dysfunction and placental abruption. Thus, the imbalance of local IGF and IGFBP-1 production might be involved in pathogenesis of abnormal pregnancy *(Figure 6)*.

IGF and fetal growth

It has been demonstrated that maternal IGF-I increased during pregnancy, especially in the third trimester [15]. IGF-I is regulated by pituitary GH, however, maternal IGF-I is believed to be regulated by placental hormones such as placental GH variant [16] rather than pituitary GH during pregnancy that is responsible for increased levels of IGF-I in the maternal circulation. Free IGF-I levels that are unbound to IGFBPs also increased in the third trimester suggesting that IGF-I bioactivity is increased in the third trimester as well.

It is well documented that maternal levels of IGF-I are correlated with birth weight [17]. Recent studies have demonstrated that binding activities of IGFBPs in maternal circulation was remarkably reduced during pregnancy due

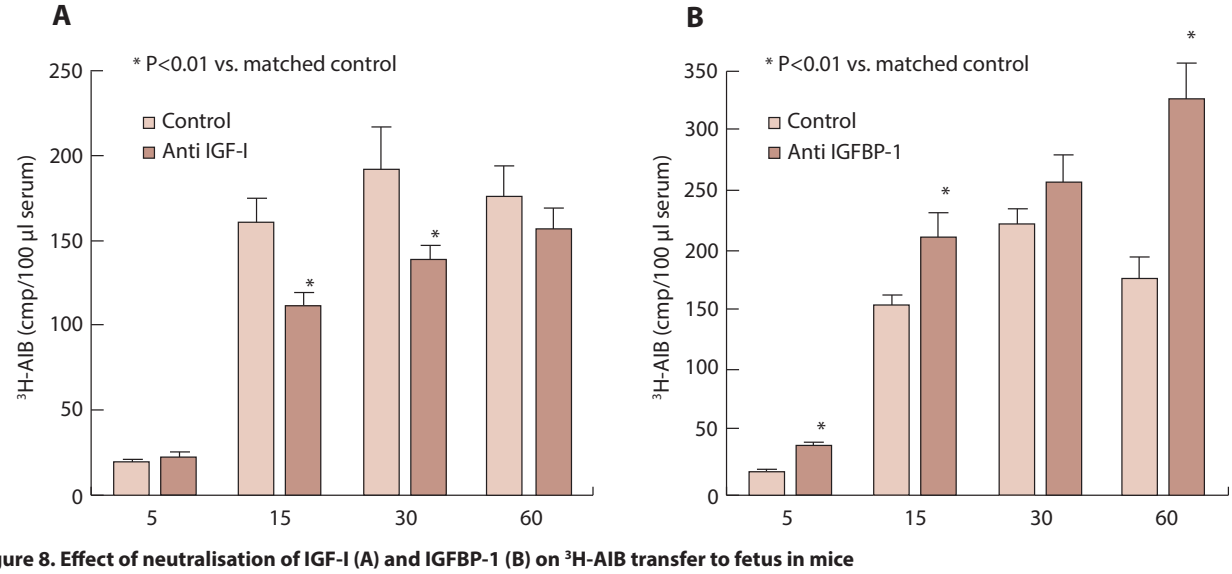

Figure 8. Effect of neutralisation of IGF-I (A) and IGFBP-1 (B) on ^{3}H-AIB transfer to fetus in mice
Anti IGF-I or IGFBP-1 is injected to pregnant mice between Day 14 and 17. On Day 18, 5µCi ^{3}H-AIB is injected to maternal mice and fetuses are removed at indicated time and sera from fetuses is pooled and radioactivity is measured.

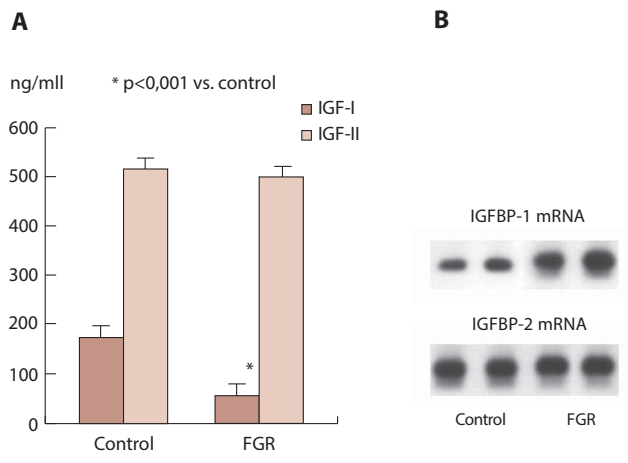

Figure 9. IGF and IGFBP-1, -2 in FGR fetus in rat
Maternal rats are starved between Day 16 and 19 and fetal blood is collected at Day 20 and measured IGF-I and IGF-II by ELISA kits (A) and mRNA for IGFBP-1 and -2 in fetal liver is analyzed by nortern blot (B).

to increased protease activity in the maternal circulation [18, 19]. When maternal IGFBPs are analyzed by ligand blot, the binding activities of IGFBP-3, IGFBP-2 and IGFBP-4 are reduced along with gestational age while binding activity of IGFBP-1 is increased throughout pregnancy *(Figure 7)* [20] and its level is inversely correlated with birth weight [15, 21]. These changes of IGFBPs are quickly returned as early as day 1 of post puerperium. Thus, maternal IGF-I and IGFBP-1 seem to play important role in fetal growth and balance of both substances may determine fetal growth. Maternal IGF-I can not to be transferred to fetal circulation through the placenta and placenta is found to contain IGF-I receptor [10, 11]. Therefore, maternal IGF-I stimulates fetal growth through the placenta presumably by activating nutrients transfer to the fetus through placenta. IGF-I stimulates 3H-glycine uptake and release by cultured trophoblast cells and IGFBP-1 inhibits stimulatory effect of IGF-I dose dependently [22]. Furthermore, fetal weight is reduced in anti-IGF-I antiserum treated mice and transfer of 3H-aminoisobutyric acid (3H-AIB) to fetus that is injected to maternal mice is also decreased. In contrast, fetal weight and transfer of 3H-AIB to fetus are increased in anti-IGFBP-1 antiserum treated mice *(Figure 8)* [22] suggesting that fetal growth and 3H-AIB transfer are accelerated by the immunoneutralization of IGFBP-1. Many studies indicate that IGFBP-1 inhibits biological action of IGF-I [13, 14, 23, 24] and this inhibitory action of IGFBP-1 is reported to be achieved by inhibiting binding of IGF-I to its receptors [25, 26]. Thus, maternal IGF-I stimulates fetal growth by activating placental transport system that increases in nutrient supply from mother to fetus. In contrast, maternal IGFBP-1 inhibits fetal growth by inhibiting IGF-I access to its receptor on placenta thereby suppressing IGF action on placenta and the imbalance of maternal IGF-I and IGFBP-1 levels might be involved in pathogenesis of fetal growth restriction (FGR).

As observed in maternal circulation, fetal circulating IGF-I is positively [27] and IGFBP-1 is negatively [28, 29] correlated with birth weight. Fetal IGF-I and IGFBP-1 levels are independent from their mother and regulated by nutritional condition. Major production site of IGFBP-1 in fetus is liver and fetal rat liver cell culture system shows that IGFBP-1 in medium is increased in the absence of glucose and amino acids in the medium [30] suggesting that fetal IGFBP-1 is increased in poor nutritional condition in vitro. A part of molecular mechanism at transcriptional level by which nutritional factors regulate IGFBP-1 production is becoming clear. It is well known that insulin response element (IRE) and glucocorticoid response element (GRE) exist in promoter gene of IGFBP-1 that inhibits and stimulates IGFBP-1 production, respectively [31, 32]. In addition, it become clear that amino acid response element exists between – 112 and –81 bp from the cap site that includes IRE and GRE region [33]. Among various kind of amino acids, levels of

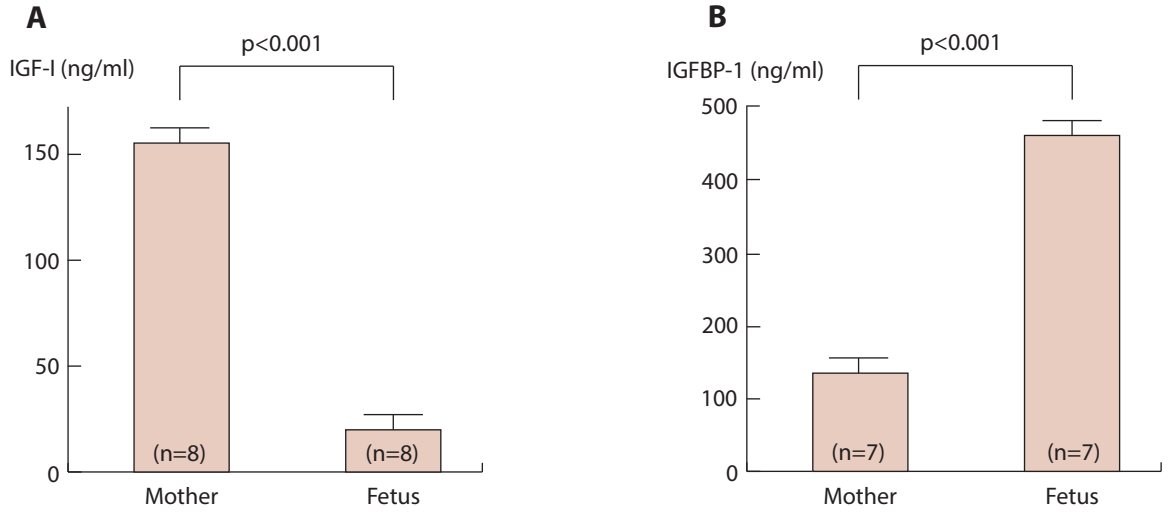

Figure 10. Circulating IGF-I and IGFBP-1 levels in mothers and their fetuses
Maternal blood and cord blood from their fetuses are collected at term delivery and IGF-I (A) and IGFBP-1 (B) are measured by ELISA kits.

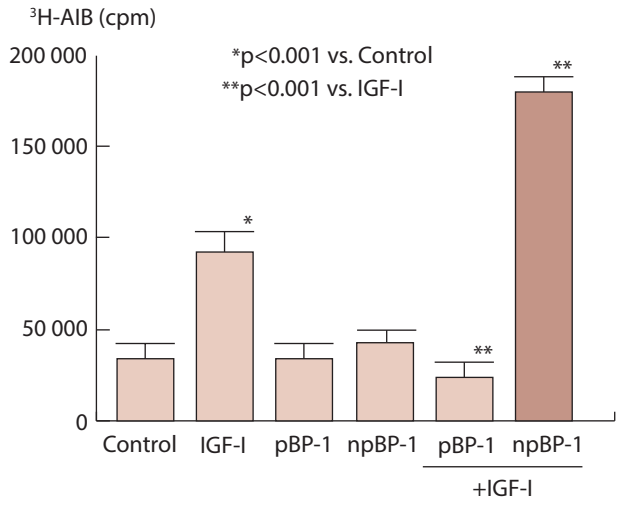

Figure 11. Effect of IGFBP-1 phosphoisoforms on IGF-I-stimulated ^{3}H-AIB uptake
Phosphorylated (pBP-1) and nonphosphorylated (npBP-1) in pooled amniotic fluids are separated by anion exchange column of HPLC. Fibroblast cells derived from term placenta are cultured in the presence or absence of 10 nM IGFBP-1 phosphoisoforms for 24hr and further incubate with or without 10 nM IGF-I for 3 hr followed by incubation with 1μCi of ^{3}H-AIB for 30 min. Incorporated redioactivity into cells is counted in a scintillation counter after solubilization.

branched chain amino acids (BCAA) in cord sera are selectively decreased in small for gestational age (SGA) infants compared to those in appropriate gestational age (AGA) infants [34]. Deprivation of BCAA stimulates IGFBP-1 production in various cell culture system [35, 36] suggesting that deficiency of BCAA in FGR fetus might be involved in pathogenesis of FGR. Since regulation of protein synthesis by BCAA is mediated by mammalian target of rapamycin (mTOR) signaling pathway [37], IGFBP-1 production might be controlled by this signaling pathway. These results suggest that fetal IGFBP-1 is regulated not only by hormones but also by nutritional factors. In vivo experiment also suggests nutritional regulation of IGFBP-1 in fetus. Rat FGR fetus by maternal starvation by which fetal weight was reduced to 65% of control shows reduced IGF-I but not IGF-II levels in the circulation. In contrast, increased mRNA for IGFBP-1 in fetal liver is observed in FGR fetus while there is no difference in IGFBP-2 mRNA between control and FGR fetus *(Figure 9)* suggesting that increased IGFBP-1 in FGR fetus is regulated at transcriptional level. Thus, FGR may not be passive reaction of fetus corresponding to decrease in maternal nutrients supply but may be active, self-protecting action to survive themselves.

Phosphoisoforms of IGFBP-1 in mother and fetus

Levels of IGF-I in the fetal circulation are extremely low while levels of IGFBP-1 are high compared to those of maternal circulation *(Figure 10)*. A contradiction between fetal developmental speed and high levels of IGFBP-1 and low levels of IGF-I in fetus suggest that the mechanism in the fetus that can mediate fetal remarkable growth is different from those in maternal side. Recently phosphorylated forms of IGFBP-1 have been reported [38] in which three serine residues in the molecule can be phosphorylated [39]. Although non-phosphorylated and phosphorylated forms of IGFBP-1 have identical molecular weight, these isoforms can be separated based on difference of electrical charge of each molecule by non-denaturing gel electrophoresis and anion exchange chromatography [40] and one non-phosphorylated and four to five phosphorylated IGFBP-1 are identified. Phosphorylated IGFBP-1 has higher affinity for IGF-I than non-phosphorylated IGFBP-1 [38, 39] and interestingly, IGF-I-stimulated 3H-AIB uptake by cultured fibroblast cells derived from term placenta is inhibited by phosphorylated IGFBP-1 while non-phosphorylated IGFBP-1 enhances IGF-I action *(Figure 11)* [41, 42] suggesting that non-

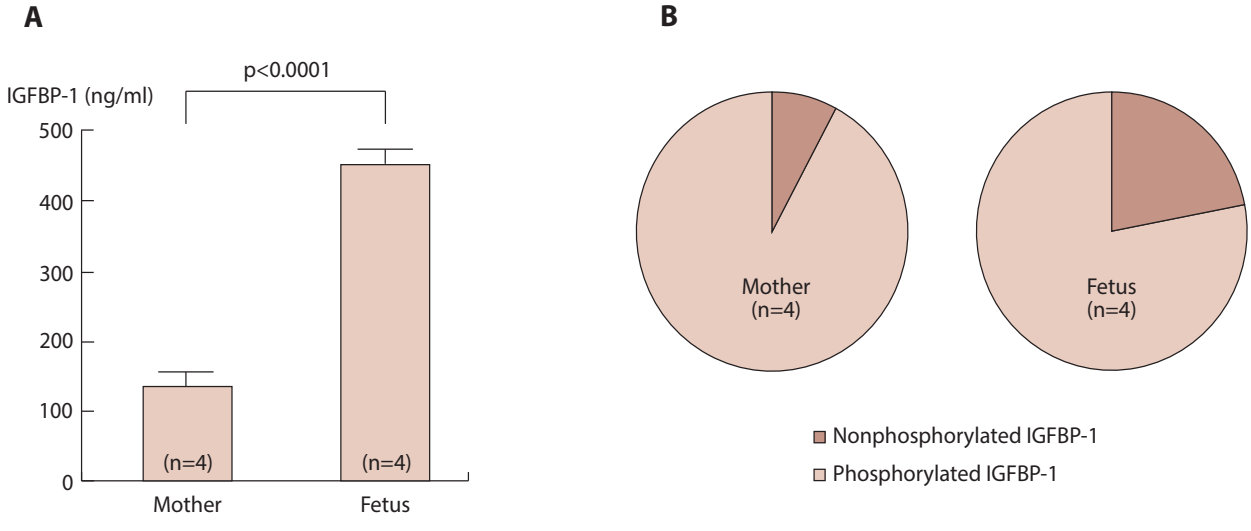

Figure 12. IGFBP-1 phosphoisoforms in mothers and their fetuses
Blood smples are collected form mothers and their fetuses at delivery between 28 and 34 weeks gestation. Total IGFBP-1 is measured by ELISA (A). Phosphoisoforms of IGFBP-1 are separated by anion exchange column of HPLC and IGFBP-1 in each fractions is measured by ELISA and expresses as percent of total IGFBP-1 (B).

Table 1. Profiles of IGFBP-1 phosphoisoforms in AGA and SGA fetuses at term

	AGA (n=15)	SGA (n=10)
Gestational age (wks)	37.8±1.7	38.4±2.6
Birth weight (g)	3108±198	2317±114[a]
Total IGFBP-1 (ng/ml)	105.5±12.3	255.5±25.9[b]
npIGFBP-1	36.7±7.9	38.4±5.8
pIGFBP-1 (ng/ml)	68.8±9.4	217.1±25.6[b]
npIGFBP-1/ total IGFBP-1 (%)	34.8±3.9	15.0±2.6[c]

Cord blood samples are collected at delivery and phosphoisoforms of IGFBP-1 are separated by anion exchange chromatography. Levels of IGFBP-1 in each fraction are measured with an immunoradiometric assay kit

[a]p<0.005; [b]p<0.00005; [c]p<0.0005 compared to corresponding values in AGA fetuses

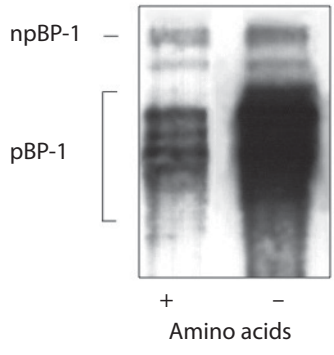

Figure 13. Effect of amino acids on IGFBP-1 phosphoisoforms release by cultured rat fetal liver cells
Rat fetal liver cells are cultured in the presence or absence of amino acids in the medium for 24 hr and medium is concentrated and subjected to non-denaturing polycrylamide gel electrophoresis. Nonphorylated (npBP-1) and phosporylated (pBP-1) IGFBP-1 are then analyzed by immunoblot

phosphorylated and phosphorylated IGFBP-1 have absolutely different biological effect on IGF action. Similar opposite effects of phosphoisoforms of IGFBP-1 on IGF-I action have been reported in vitro and in vivo [43, 44]. Phosphoisoforms of IGFBP-1 separated by anion exchange chromatography demonstrates that the proportion of non-phosphorylated IGFBP-1 to total IGFBP-1 is significantly higher in infants than their mothers *(Figure 12)* although total amounts of IGFBP-1 are higher in infants than in mothers. This may suggest that biological activity of IGF is higher in fetus compared to their mothers and it may be a possible explanation for remarkable growing speed observed in fetus even in high levels of IGFBP-1.

IGFBP-1 is phosphorylated intracellularly by various kinases in vivo and in vitro and phosphorylated IGFBP-1 is specifically increased in a catabolic state such as severe trauma or diabetes mellitus [45, 46]. Only phosphorylated forms of IGFBP-1 are increased when rat fetal liver cells are cultured in the absence of amino acids *(Figure 13)*. In human, total IGFBP-1 levels are higher in SGA fetuses than in AGA fetuses and phosphorylated IGFBP-1 was higher in SGA fetuses than in AGA fetuses although non-phosphorylated IGFBP-1 levels are similar between two groups *(Table 1)* [42, 47]. Thus, biological activity of IGF-I in SGA fetus is presumed to be more suppressed than in AGA fetus. These phenomena also support self-protecting mechanism in fetus by which fetuses restrict their growth to survive in malnutritional environments.

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