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THE GROWTH HORMONE GENE CLUSTER: PHYSIOLOGICAL ACTIONS AND REGULATION DURING PREGNANCY

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given to the roles for these hormones in the regulation of fetal growth and metabolism and to the hormonal and other factors that regulate their expression. Particular attention is given to studies from the author's laboratory. Several excellent comprehensive reviews have been published over the past few years that focus on the biology of the individual genes of the cluster.^{1,2}

INTRODUCTION

This manuscript reviews selective aspects of the molecular biology and physiology of the human growth hormone cluster genes during pregnancy. Special emphasis is

THE HUMAN GROWTH HORMONE CLUSTER

The human growth hormone gene cluster consists of the genes that code for placental lactogen (PL; also known as chorionic

From The Editor's Desk 2009

"You cannot build a house for last year's summer." This Ethiopian proverb may be applicable to the state of *GGH* on its 25th anniversary. Since 1984, when the journal was conceived, the editorial board has worked tirelessly to produce a journal of high scientific value, publishing original lead articles and reviews of the most important publications in the field with erudite editorial comments. We have pushed against our deadlines and provided our readers a high quality publication—without commercial bias. It has been gratifying, and *GGH* has become a very well appreciated source of information to pediatric endocrinologists and other specialists interested in the field. We have remained on top of the medical specialty and have been innovative—8 years ago we launched the journal on line. We now reach more than 11,000 subscribers worldwide and almost 500 readers every single day! We have told ourselves, and our readers have acknowledged, it has been *GGH* at its best; and, since its inception it has been treasured.

However, in the new world of endless headlines and multiple sources of information an educational journal like ours has become difficult to fund. Scientific breakthroughs are published in *The New York Times* and repeated endlessly on cable news. Most scientific journals now contain editorials and review articles and derive strength from the members of the society that funds the journal. They often publish targeted supplements supported by industry. Pharmaceutical companies utilize multiple means to market their products directly to physicians and have turned away from supporting an educational journal like *GGH*, or fallen on hard times themselves. We have made major efforts to continue publishing the journal and have sought support from multiple sources including the pediatric endocrine societies, and industry—to no avail.

We believe that while there is no shortage of information, there is a scarcity of objective, unbiased insight into specific issues in pediatric endocrinology. This has been *GGH's* niche and this is why it should continue informing our very large audience. But our strategy is no longer sustainable as sponsors utilize direct means of reaching and targeting their prospects. Therefore, this *GGH* issue will be the last one of the series that you have enjoyed for 25 years. You will be hearing from us if we are able to obtain the funding necessary to provide you with a valuable unbiased educational resource.

Your thoughts will be welcome at FimaLifshitz@GGHjournal.com.

Respectfully,
Fima Lifshitz, MD
Editor-in-Chief

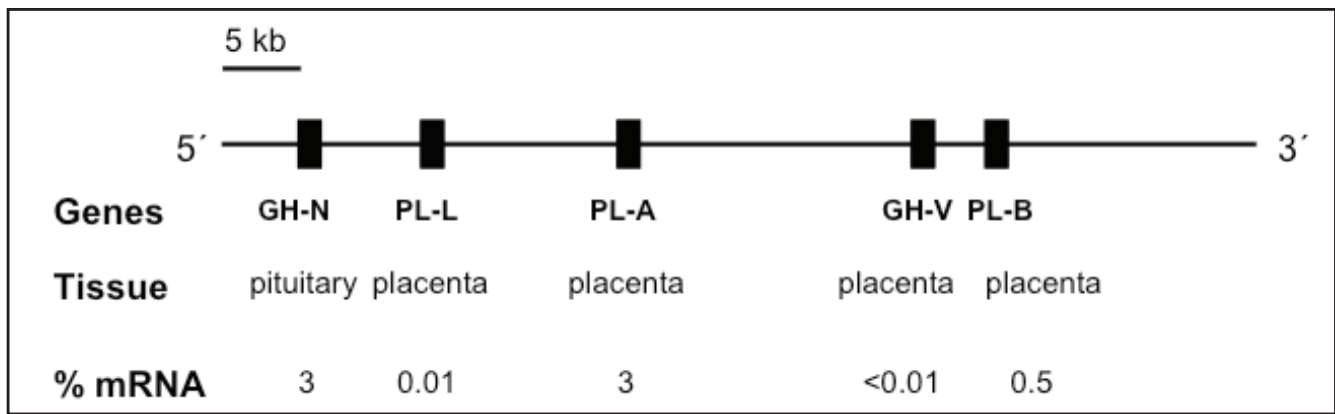


Figure 1. The human growth hormone gene cluster.

The orientation and tissue-specific expression of the five genes comprising the cluster are shown from 5' to 3'. Also shown is the percentage of total mRNA for each gene in the placenta or pituitary. The abundance of hPL greatly exceeds that of hGH-V.

somatomammotropin, CS), growth hormone variant (GH-V; also known as placental growth hormone) and growth hormone normal (GH-N; also known as pituitary growth hormone). The cluster contains five genes, three PL and two GH genes that evolved from a common ancestral precursor by recombination events involving moderately repeated sequences. The cluster spans 66 kb on chromosome 17 (q22-q24).³ The individual genes are organized in the same transcriptional orientation and are each composed of five exons and four introns. The order of the genes from 5' to 3' is GH-N, PL-L, PL-A, GH-V, and PL-B (Figure 1). The PL genes and GH-V are expressed exclusively in the placenta, and GH-N is expressed exclusively in the pituitary. As discussed below, the expression of the GH cluster is controlled by a locus control region (LCR) that is located 14.5 to 32 kb upstream of the GH-N gene.^{4,5}

PL and GH-V are synthesized and secreted by the trophoblast layer of the placental villus, and the expression of the genes is tightly coupled to placental differentiation. The trophoblast layer is composed of two cell types—multinucleated syncytiotrophoblast cells and the underlying mononuclear cells that are the precursor cells that proliferate and fuse to form the overlying syncytium.⁶ PL and GH-V are not expressed by the cytotrophoblast cells but are expressed as the cells undergo differentiation to a syncytiotrophoblast phenotype. Because of the tight coupling between GH gene cluster expression and villous trophoblast differentiation, the expression of the cluster genes in the placenta is regulated in large part by transcription factors and other signaling molecules that are critical for trophoblast differentiation.

The members of the GH gene cluster share 91% to 99% sequence identities throughout the coding regions and within a 500 bp region immediately upstream of the genes (for review see 7). PL-A and GH-V are alternatively spliced and encode 22 and 26 kD gene products, while PL-B encodes a single 22 kD protein product. The PL-A and PL-B mRNAs are 98% homologous and encode

identical mature proteins that are 85% identical to GH-N. The mRNAs for PL-A and PL-B are among the most abundant mRNAs in the placenta, comprising approximately 3.5% of the total mRNA. The PL-A gene is normally expressed at levels three to six times greater than the PL-B gene, probably due to differences in stability of the two mRNAs. The expression of the mRNA encoding PL-L increases towards term;⁸ however, the PL-L protein product(s) is not secreted. The amino acid sequence of GH-V and GH-N differ in fifteen positions, thirteen of which are in the mature protein and are distributed throughout the sequence.⁹⁻¹¹ The GH-N gene encodes two alternatively spliced mRNAs that are translated into 22 and 20 kD GH proteins. Although GH-N AND GH-V share striking homologies in structure, immunoassays for GH-N do not detect GH-V and visa versa. Consequently, immunoassays for GH-N cannot be used to measure GH-V.

EXPRESSION OF PL AND GH-V IN NORMAL AND PATHOLOGIC PREGNANCIES

The maternal concentrations of PL and GH-V increase markedly during pregnancy. Human PL is first detected in syncytiotrophoblast cells at 5-10 days after implantation and in maternal plasma at about six weeks of pregnancy.¹² Its concentration then increases linearly until weeks 32-35 of gestation when peak concentrations of 5000 to 7000 ng/mL are attained.¹³ The secretion rate near term is about 1.0 gm/day, a rate considerably greater than that of any other polypeptide hormone. Throughout pregnancy, the plasma concentration of PL in the mother correlates with placental mass and is greater in multiple than in singleton gestations. In addition, the pattern of PL secretion during pregnancy roughly parallels the marked increase in maternal plasma insulin-like growth factor (IGF)-I concentrations that normally occurs in pregnancy. Direct measurement of the plasma concentrations of PL in the human fetus in vivo reveals a rise in fetal PL levels from a mean of 5 ng/mL at 20 weeks of gestation to a mean of 20-30 ng/mL at birth.¹⁴ Since radiolabeled PL does not cross the placenta from the maternal

to the fetal circulations, PL appears to be secreted directly into fetal blood.

Aberrations of PL secretion have been detected in many common pathologic conditions of pregnancy, including diabetes mellitus, pre-eclampsia and hypertensive vascular disease.¹⁵⁻¹⁸ In one large series of patients, a single PL concentration below 4 mcg/mL in the last five weeks of pregnancy was associated with 30% risk of fetal distress or neonatal asphyxia. Low PL concentrations on two separate occasions during the last five weeks were associated with a fetal risk of 50% and low concentrations on three occasions with a risk of 71%.¹⁹ In another series of patients, PL concentrations below 4 mcg/mL were detected in 47 of 98 pre-eclamptic patients.²⁰ Perinatal mortality in the neonates born to the mothers with low PL concentrations was 13% and intrauterine growth retardation was noted in 57% of the neonates.

The lower than normal plasma concentrations of PL and other placental hormones in pregnancies complicated by intrauterine growth retardation (IUGR), pre-eclampsia and other pathologic conditions are probably due in large part to the placental hypoxia and decreased placental mass that is usually found in these conditions. In pre-eclampsia, for example, there is shallow invasion of cytotrophoblast cells into the endometrium, myometrium and spiral arteries of the uterus that results in decreased exchange of substrates, oxygen, hormones and other factors across the placenta. Consequently in pre-eclampsia, IUGR and other pathologic conditions of pregnancy associated with decreased PL, there are multiple factors that contribute to the growth failure of the fetus; and it is not possible to determine the relative contribution of decreased PL concentrations to the growth retardation.

GH-V is first detected in the maternal circulation at about 10 weeks of pregnancy, reaching a maximum in the third trimester of approximately 20-60 ng/mL, becoming the predominant form of GH in maternal serum throughout the latter half of pregnancy.^{21,22} GH-V is not detected in fetal serum at any time during pregnancy,²¹ indicating that the effects of the hormone on fetal metabolism or growth must be mediated indirectly through actions on maternal and possibly uteroplacental tissues. In contrast, the fetal circulation contains abundant amounts of GH-N, the levels of which rise to a maximum at mid gestation (33.6 ± 2.1 ng/mL by periumbilical blood sampling)²³ with a slow decline to levels approximating 20 ng/mL at term. There is a positive correlation between GH-V concentrations and the birth weight of the fetus; however, GH-V levels in the late second trimester or early third trimester are not predictive of fetal birth weight. Higher GH-V levels have been reported in pregnant women carrying female fetuses, suggesting a gender influence. Both GH-V and PL levels are increased in multiple pregnancies.

Mittal and co-workers have shown that preeclampsia is associated with higher concentrations of placental growth hormone in both the maternal and fetal circulations compared to normal pregnancy.²⁴ They have also shown that patients with preeclampsia plus small for gestational age (SGA) have lower maternal serum concentrations of GH-V than preeclampsia patients without SGA. Little is known about the regulation of GH-V production in abnormal pregnancies. However, recent studies demonstrate that maternal GH-V levels are reduced in pregnancies associated with IUGR.^{22,23,25}

In contrast, GH-N concentrations during gestation remain relatively stable at 4 to 6 ng/mL. Fetal PL concentrations near term are 80 to 125 ng/mL, while GH-V is not detected in fetal plasma. Although GH-N levels remain low in the maternal circulation during pregnancy, GH-N is detected at relatively high concentrations in the fetus. GH-N concentrations in fetal plasma at term are 28 to 38 ng/mL, significantly greater than those detected in maternal plasma.

PHYSIOLOGICAL ACTIONS OF PL AND GH-V

Both PL and GH-V bind to sommatotrophic and lactogenic receptors on a wide variety of tissues and have biological actions in many tissues, including liver, bone, blood cells and placenta. The potency of GH-V in growth-promoting assays is about 7-fold greater than that of PL; and the lactogenic potencies of the two hormones are comparable to that of prolactin. The rise in IGF-I levels in response to the placental hormones likely induces growth of maternal tissues, including the uterus, breast, and thyroid gland. Actions on the heart and kidney may increase cardiac output and maternal blood volume. Recent studies have shown that hGH-V regulates the invasion of extravillous trophoblast cells in the uterus,²⁶ but it is not known whether PL acts in an autocrine or paracrine manner to regulate placental development and/or function.

Maternal intermediary metabolism undergoes striking changes during pregnancy. In early and mid-gestation, body fat accumulates, while, in mid- to late gestation, the sensitivity to insulin declines and the mother develops postprandial hyperglycemia, hypertriglyceridemia and hyperinsulinemia. Prolonged fasting in late pregnancy leads to exaggerated production of free fatty acids and ketone bodies. These adaptations are thought to insure the continuous supply of glucose and amino acids to the fetus, thereby promoting fetal growth. Several lines of evidence strongly suggest that PL and GH-V play important roles in the metabolic adaptation to pregnancy. PL increases food intake and stimulates glucose uptake, glucose oxidation and the incorporation of glucose into glycogen, glycerol and fatty acids in isolated rat adipocytes, facilitating lipid and glycogen accumulation in the mother in early and mid-pregnancy pregnancy and during the fed state. PL, in concert with prolactin, progesterone, glucocorticoids

and other hormones, reduces insulin sensitivity and induces carbohydrate intolerance *in vivo*,^{27,28} and stimulate ³H-thymidine incorporation, insulin gene transcription, insulin production and glucose-dependent insulin secretion in pancreatic islet cells.^{29,30} These actions of PL therefore contribute to postprandial hyperglycemia and hyperinsulinemia in the pregnant mother in mid to late pregnancy. PL also increases the basal rates of lipolysis in adipocytes and the plasma concentrations of nonesterified fatty acids, ketones and glycerol. The mobilization and utilization of maternal free fatty acids for energy spares maternal glucose for the fetus.

Several lines of evidence suggest that PL also has direct anabolic effects on fetal metabolism that promote fetal growth. PL is present in the fetal circulation in relatively high concentrations, binds to fetal tissues that are critical for fetal growth, and has direct growth-promoting actions on fetal tissues. The administration of PL to hypophysectomized rats increases tibia epiphyseal growth and plasma IGF-I concentrations with a potency approximately 5% to 10% that of GH. Furthermore, the placental hormone stimulates amino acid uptake, DNA synthesis and IGF-I production in cultured human fetal myoblasts, fibroblasts and hepatocytes.³¹⁻³³ The effects of PL on ³H-thymidine incorporation and amino acid transport are blunted, though not abolished, by an antiserum to IGF-I, suggesting that the action of PL is mediated in part through the paracrine release of IGF-I.

PL and prolactin also stimulate DNA synthesis and insulin production in fetal and neonatal pancreatic explants and promote the formation of islet-like cell clusters in cultured pancreas cells.^{30,34,35} These findings strongly suggest roles for PL in the induction of islet cell growth and insulin production in the late-gestational fetus. Other possible roles for PL in the fetus include the production of fetal adrenocortical steroid hormones and development of the fetal lung. PL also stimulates DNA synthesis in human mammary epithelial cells and growth of ductal epithelium, suggesting that the hormone may facilitate mammary development prior to delivery. A summary of the biological actions of PL in the mother and fetus is shown in Figure 2.

On the other hand, several lines of evidence indicate that GH-N plays only a limited role in fetal linear growth. Patients with isolated GH deficiency, pituitary aplasia or anencephaly have only minimal or modest (and inconsistent) reductions in birth length.³⁶ Furthermore, a deficiency of GH in experimental animals has little or no effect on fetal growth. For example, dwarf mice deficient in pituitary GH have normal tail lengths at birth and modest (14%) reductions in birth weight, though serum IGF-I and IGF-II concentrations are reduced significantly.³⁷ Decapitation, encephalotomy or hypophysectomy of fetal rabbits, rhesus monkeys, rats, mice, or pigs is not accompanied by fetal growth failure or reductions in serum IGF-I concentrations, and electrolytic destruction of the ovine fetal medial-

basal hypothalamus with concomitant GH deficiency has no effect on fetal plasma IGF-I or IGF-II concentrations (reviewed in 38). Conversely, an excess of fetal GH is not accompanied by fetal overgrowth.

Although GH-N may have only a limited effect on the longitudinal growth of the fetus, the hormone appears to have important effects on fetal metabolism and development. For example, clinical experience substantiates a role for GH-N in perinatal carbohydrate metabolism. The neonatal hypoglycemia may result in part from heightened sensitivity to insulin; however, deficient storage of glycogen in fetal liver may also play a role because GH stimulates glycogen synthesis and inhibits glycogenolysis³⁹ in

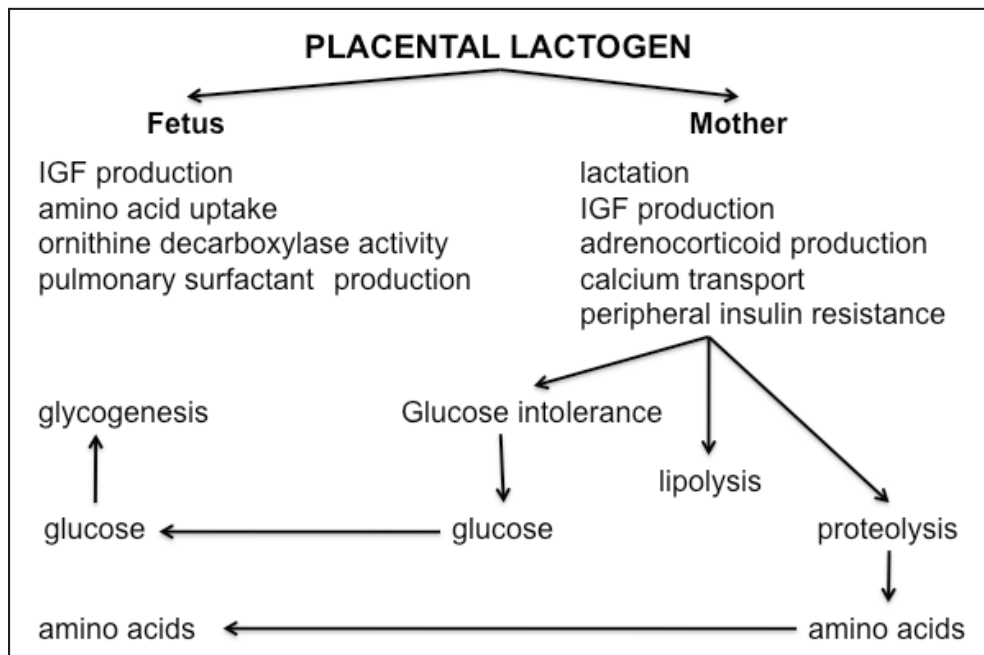


Figure 2. The biological actions of PL in the mother and fetus.

PL has direct effects on fetal and maternal tissues that modulate fetal growth and metabolism. The induction of peripheral insulin resistance in the mother leads to glucose intolerance with resulting hyperglycemia as well as to an increase in lipolysis and proteolysis. The net effect of these changes is the transport of glucose and amino acids to the fetus and the stimulation of glycogenesis and protein synthesis in the fetus. PL also induces IGF production in the mother and fetus and stimulates lactation in the mother and pulmonary surfactant production in the fetus. The enzyme ornithine decarboxylase is important for the synthesis of DNA, RNA and protein.

isolated hepatocytes from fetal sheep and fetal rats. GH also stimulates DNA synthesis and IGF-I production in isolated human fetal hepatocytes as well as DNA synthesis, insulin production and glucose-dependent insulin secretion in isolated pancreatic islets from human adults and fetal and neonatal rats and mice. These latter observations implicate a role for GH in perinatal islet development and function. The high prevalence of micropenis in newborn males with GH deficiency or GH resistance^{40,41} implicates a role for pituitary GH in the regulation of human phallic growth in utero.

REGULATION OF THE HUMAN GROWTH HORMONE GENE CLUSTER

As discussed below, the GH cluster is controlled by a remote LCR that is located 14.5 to 32 kb upstream of the GH-N gene.^{4,5} The LCR contains five hypersensitive sites (HSI-HSV), which are short regions of chromatin detected by supersensitivity to cleavage by DNase 1. These sites, which are only found in active genes, appear before the initiation of transcription and are generated as a result of the binding of transcription factors that displace histones after binding to DNA within the hypersensitive site. Closely linked HSI and HSII are pituitary specific, HSIV is placental specific, and HSIII and HSV are present in both tissues. HSV and HSIII, at -32 kb and -28 kb, are detected in pituitary somatotrope and placental syncytiotrophoblast cell chromatin; HSIV, at -30 kb, is specific to syncytiotrophoblast cell chromatin; and HSI and HSII, at -14.5 kb to -15.5 kb, are specific to somatotrope chromatin. The GH LCR and the GH-N promoter are encompassed by a continuous 32 kb pituitary-specific domain of acetylated histones H3 and H4 with a central peak located at HSI. Histone acetylation is linked to transcriptional activation; and histone acetyltransferases (HATs) and histone deacetylases (HDACs) are recruited to promoters through physical interaction with sequence-specific transcription factors. Site-specific inactivation of HSI results in loss of acetylation throughout this domain, loss of critical transfactor occupancy at the GH-N promoter, and a 20-fold reduction in GH-N expression. Thus, HSI plays an essential role in the establishment of the acetylated domain and in activation of GH-N transcription in the pituitary.

Histone acetyltransferase (HAT) activity recruited to HSI establishes a continuous 32 kb domain of histone acetylation connecting the LCR and the GH-N promoter. This acetylated domain facilitates transfactor binding at the GH-N promoter and transcriptional activation of GH-N. Activation of the placental genes in the term placental syncytiotrophoblast cells is marked by activating histone modifications that are restricted to HSV-HSIII and to the placental genes; the regions between, which include HSI,II and the GH-N gene, remain unmodified. Based on the present knowledge of cellular differentiation and epigenetic alterations, it seems reasonable to propose

that chromatin structures in the placenta are altered during the terminal transition from cytotrophoblast cells to syncytiotrophoblast cells to result in robust induction of gene expression from the GH cluster.

Gene activation during cytotrophoblast cells differentiation to a syncytiotrophoblast cell phenotype is initiated by H3K4 methylation of HSIII-HSV of each individual placental gene repeat (PGR) unit.⁴² Subsequent transcriptional activation is accompanied by acetylation of histones H3 and H4 encompassing the entire placenta-expressed region of the cluster. The distribution and progression of chromatin modifications suggests that each PGR independently initiates transcription. Initial activating chromatin modifications are nucleated within the individual PGR units; and subsequent transcriptional induction relies on additional determinants and more extended chromatin modifications.

REGULATION OF PL AND GH-V EXPRESSION

Although *in vivo* studies have provided information about the regulation of PL and GH-V secretion, most information about the expression of these hormones has been obtained using primary cultures of human cytotrophoblast cells or explant cultures. The primary cytotrophoblast cells, which are prepared by enzymatic dispersion of term or pre-term placental tissue, undergo spontaneous aggregation, syncytialization and terminal differentiation and express genes normally expressed by syncytiotrophoblast cells, including PL and GH-V.

Using these *in vitro* model systems, many factors have been shown to induce trophoblast differentiation and the expression of PL and GH-V. These factors include epidermal growth factor,⁴³ chorionic gonadotropin,⁴⁴ leukemia inhibitory factor,⁴⁵ colony stimulating factor-1,⁴⁶ IGF-I,⁴⁷ cyclic AMP,⁴⁸ members of the transforming growth factor β superfamily,⁴⁹ the Wnt/ β -catenin pathway,⁵⁰⁻⁵² the transcription factors PPAR γ ,⁵³ Ikaros,⁵⁴ GATA-2/3,⁵⁵ and several other factors in the differentiation process. Oxygen has also been shown to be a critical factor in the differentiation process and the induction of the GH cluster genes (for summary see 56). Low oxygen tension directs placental differentiation along the extravillous trophoblast cell pathway in which cytotrophoblast cells invade the uterus. Greater oxygen tension directs differentiation along the villous trophoblast cell pathway and the formation of the trophoblast layer that lines the placental villus. Recent studies from the author's laboratory have also demonstrated a critical role for the transcription factor TFAP2A (also known as AP2, activator protein 2) in syncytiotrophoblast formation and the induction of PL and GH-V.^{57,58}

Knockout experiments in the mouse have identified many transcription factors that are important in the differentiation of the various cell types constituting the murine placenta,⁵⁹⁻⁶¹ including HOXB6, HOXC5, HOXC6,

HOX3E, HB24, GCM1, GAX, MSX2, DLX4, Pit-1, HAND1, TF-1, TEF5, c-Ets1 and several other transcription factors, many of which are helix-loop-helix (bHLH) proteins. ID-2, a member of a family of inhibitors of bHLH binding, acts in trophoblast cells as a dominant/negative bHLH transcription factor;⁶² and constitutive overexpression prevents differentiation of the cells. However, the roles for homologs of these transcription factors in human placental development are not known.^{63,64}

PL expression

At present, the specific hormonal and metabolic factors that regulate the secretion of PL are incompletely PL understood. Although PL has striking homologies in structure and function to GH-N, the factors that regulate the expression of the two hormones are different. For example, changes in circulating levels of free fatty acid concentrations, amino acids such as arginine, estrogens, oxytocin, prostaglandins, epinephrine, TRH, GnRH, dopamine and glucocorticoids do not effect modulate PL secretion. While changes in blood glucose concentrations modulate GH-N secretion, glucose does not appear to have consistent effects on PL secretion in the mother. Most investigators have failed to demonstrate significant changes in PL concentrations following glucose administration or insulin-induced hypoglycemia. However, a significant decrease in plasma PL concentrations was noted in one study following two intravenous infusions of glucose one hour apart or the continuous infusion of glucose over several hours. Several studies have reported a 30%-40% increase in plasma PL concentrations in women fasted 84-90 hours during weeks 16-22 of gestation (prior to therapeutic abortion⁶⁵). Interestingly, angiotensin II has also been shown to stimulate PL secretion *in vitro*.⁶⁶

Studies of the regulation of PL gene expression suggest a role for autocrine/paracrine factors in the regulation of PL gene expression. 1,25-dihydroxyvitamin D₃, interleukin (IL)-6 and IL-1, all of which are synthesized and secreted by syncytiotrophoblast cells, stimulate the synthesis and release of PL by trophoblast cells.^{67,68} 1,25-dihydroxyvitamin D₃ stimulates PL gene expression via the vitamin D receptor that binds to a composite nuclear hormone receptor site on the PL promoter.⁶⁹ Retinoic acid and thyroid hormone also stimulate PL gene expression via the binding of RARA and TRB receptors to the same composite site.⁷⁰ The action of IL-6 is mediated, at least in part, by the transcription factor NF-IL6 that binds to three consensus NF-IL6 elements on the distal PL promoter.⁷¹ It is likely that other cytokines and nuclear hormone receptors are also involved in the regulation of PL expression.

Recent studies strongly suggest a novel physiologic role for high density lipoproteins (HDL) in the regulation of PL gene expression during pregnancy.⁷² The stimulation appears to be due primarily to pre- β HDL, a minor

component of the total HDL in the circulation that is much smaller in size than the major circulating form (α -HDL) but which contains a much higher apolipoprotein (apo) A-I/lipid ratio. During pregnancy, pre- β concentrations in maternal plasma increase markedly with a pattern that parallels that of PL.⁵⁴ Pre- β HDL concentrations increase from 3% to 4% of the total HDL in the early first trimester to about 20% at term.

The stimulation by HDL is mediated by apoA-I and, to a much lesser extent, apoA-II and apoC. Amphipathic peptides that mimic the tree dimensional structure of apoA-1 also stimulate PL promoter activity and the expression of PL from cultured trophoblast cells. The action of apoA-1 is due, at least in part, by activation of adenylate cyclase and phospholipase C. ApoA-1 stimulates a time- and dose-dependent increase in MAP kinase activity. ApoA-1 has also been shown to have other non-lipid-dependent effects, including the stimulation of endothelial cell proliferation, endothelin-1 production by renal cells, and the inhibition of degranulation and superoxide dismutase activity in neutrophils. Plasma apoA-I concentrations have been reported to be significantly lower than normal in several pathologic conditions of pregnancy associated with decreased plasma PL concentrations and IUGR, including pre-eclampsia⁷³ pregnancy-induced hypertension⁷⁴ and insulin-dependent diabetes mellitus.⁷⁵ Whether the low apoA-I concentrations contribute to the decrease in PL secretion in these patients is unknown.

GH-V expression

The secretion of GH-V, like of GH-N, is induced by hypoglycemia and suppressed by glucose and is regulated by cAMP. However, unlike GH-N, GH-V is released tonically and is not regulated by growth hormone releasing hormone, ghrelin and somatostatin. In addition, the GH-V promoter is not regulated by the transcription factor Pit-1. Studies by Lominick and Handwerker⁷⁶ have shown that the GH-V promoter is transactivated by the transcription factors MEF2 and FOXF1 but not FOXF2. Since FOXF1 and FOXF2 bind to the same DNA binding site, the difference in the ability of the two FOX proteins to transactivate the GH-V promoter is likely due to differential binding of the proteins to one or more co-activators.

SUMMARY

The human GH cluster consists of five closely related genes. GH-V, PL-A, PL-V and PL-L are expressed exclusively in the placenta, while GH-N is expressed exclusively in the pituitary. Both PL and GH-V have growth-promoting and lactogenic activities during pregnancy. PL is detected in both the maternal and fetal circulations and has direct growth-promoting actions in both compartments. GH-V, on the other hand, is only detected in the mother. Although PL and GH-V have striking structural and biological homologies to GH-N, the

factors that regulate the expression of placental genes are different from those that regulate pituitary growth hormone. Aberrations in PL and GH-V have been noted in several pathologic conditions of pregnancy, including preeclampsia and IUGR.

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