CURRENT TOPIC

Fetal growth restriction and hepatocyte growth factor

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Fetal growth restriction remains one of the major problems currently facing obstetricians; it contributes significantly to preterm birth rates (both iatrogenic and idiopathic), together with perinatal morbidity and mortality.¹ Recent epidemiological data suggest that "prenatal programming" due to intrauterine growth restriction (IUGR) may also predispose surviving infants to diseases in adult life.²

Hepatocyte growth factor (HGF) is a ubiquitous and pluripotent cytokine with a variety of paracrine and endocrine effects that was first identified 15 years ago.³ In vitro studies have suggested that important steps in organogenesis may be mediated by HGF,⁴ and more recent in vivo "gene knockout" studies using mice constructs have indicated a crucial role for HGF and its receptor *c-met* in placental and fetal hepatic growth and development.⁵⁻⁷

Growth factors and intrauterine growth restriction

The development of the fetus is under multifactorial control: the inherent drive to body growth determined by the fetal genome is tempered by "epigenetic" or environmental factors that alter its expression.⁸ The aetiology of IUGR can therefore be divided into those factors affecting the genome itself (for example, karyotypic abnormalities such as trisomies and triploidies), and those altering its expression.

Other than fetal insulin, none of the major endocrine hormones (maternal or fetal) seems to have a direct influence on fetal growth.⁹ The current view is that locally synthesised macromolecules (for example, growth factors and cell adhesion molecules), acting either in an autocrine or paracrine manner, regulate embryonic organ and tissue growth. The epigenetic factors associated with IUGR must therefore in some way affect these molecules or their receptors.

Clinically, other than chromosomal abnormalities and viral infections, most IUGR is attributed to inadequate substrate supply to the fetus. This may be due to reduced availability to the placenta itself (maternal malnutrition), or to poor placental function ("placental insufficiency"). From the late first trimester onwards, the human fetus is entirely dependent on its placenta for supply of oxygen and nutri-

ents (and clearance of other molecules). Poor placental function can therefore become a rate limiting step with regard to fetal growth, particularly towards the end of gestation when fetal metabolic demands are greatest.

Maternal microvascular diseases such as hypertension, diabetes, systemic lupus erythematosus and the antiphospholipid syndrome may impair placental development and function, but these are thought to account for less than half the cases of placental insufficiency.¹ In most cases of IUGR associated with placental insufficiency the underlying causes remain unknown, despite clinically relevant placental pathology such as impaired endovascular trophoblast invasion, abnormal angiogenesis, and villous maldevelopment.^{10, 11}

However, there is evidence that micro deletions or alterations in certain "homeobox" genes may directly or indirectly affect the transcription of growth factors/cytokines.⁸ These may in turn alter the interaction between the maternal and fetal vasculature and trophoblast, which may reduce growth potential. Such genes may also affect organogenesis and organ growth in utero.⁸

The expression of growth factors may therefore be altered in response to environmental factors such as oxygen tension or malnutrition, or there may be a primary abnormality of specific growth factors and/or their receptors, leading to malplacentation and possibly affecting other fetal organs.

Hepatocyte growth factor

Hepatocyte growth factor is a potent multifunctional cytokine that acts variously as a mitogen, morphogen, motility factor and cytotoxic agent for a vast spectrum of cell types. The existence of an endocrine hepatotrophic factor was first alluded to in 1949, although it was not actually discovered until four decades later.^{3, 12} Molecular sequencing revealed that HGF was identical with two other independently discovered cytokines: scatter factor, a cell dissociation factor for epithelial cells; and tumour cytotoxic factor.¹³ It became apparent that HGF had a broader spectrum of activity than a simple hepatocyte mitogen. A detailed discussion of these effects in adult tissue is beyond the scope of this review and the reader is referred to other texts.^{14, 15}

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Table 1 Tissue types identified as sources of HGF²⁰

Brain	Leukocytes	Pancreas	Spleen
Breast	Liver	Placenta	Stomach
Small intestine	Lung	Prostate	Thymus
Large intestine	Megakaryocytes	Salivary glands	Thyroid
Kidney	Ovary	Skin	

Table 2 Tissue types identified as sources of c-met^{14 15 23}

Brain	Hepatocytes	Neutrophils
Breast	Keratinocytes	Ovary
Endometrium	Kidney	Placenta
Fibroblasts	Lung	Spleen
Gastrointestinal epithelia	T & B lymphocytes	
Haematopoietic cells	Melanocytes	

STRUCTURE AND DISTRIBUTION OF HGF AND ITS RECEPTOR C-MET

Hepatocyte growth factor is secreted as an inactive, single chain, 82 kiloDalton heparin binding glycoprotein.¹⁶ It largely remains in this form in the extracellular matrix, possibly associated with heparan sulphate proteoglycans.^{17 18} Proteolytic cleavage of this precursor results in the active heterodimer. This consists of a heavy α chain (54–69 kiloDaltons) containing four kringle domains and a hairpin loop, and a light β chain (26–34 kiloDaltons) linked by a disulphide bond—all these structures being essential for its physiological activity.¹⁹ Splice variants are known to occur, with altered biological activity, but their physiological importance has yet to be elucidated.¹⁴ In situ hybridisation studies revealed the presence of HGF mRNA in a vast selection of human tissue types in cells of mesenchymal origin (table 1).²⁰

The biological actions of HGF are mediated via a 190 kiloDalton transmembrane glycoprotein known as c-met.²¹ The active molecule consists of two disulphide linked subunits (α and β), the product of proteolytic cleavage of a single chain precursor.²² The β chain is 145 kiloDalton and spans the plasma membrane, whereas the 50 kiloDalton α chain is entirely extracellular. The intracellular domain of the β subunit contains a tyrosine kinase domain and sites for autophosphorylation through which the cellular effects of c-met are mediated.¹⁴ Inactive truncated forms of c-met, lacking the intracellular tyrosine kinase domain, are known to exist. In situ hybridisation studies showed c-met mRNA had a similar tissue distribution to HGF (table 2),^{14 15 23} but analysis of the cell types involved showed that c-met was produced and expressed predominately by cells of embryonic epithelial origin.⁴

EFFECTS OF HGF/C-MET

Activation of c-met by hepatocyte growth factor leads to dimerisation of the receptor, followed by autophosphorylation of several intracellular messengers which are thought to mediate its subsequent effects.¹⁴ The exact nature of the cellular response to HGF depends on the cell type.

The mitogenic properties of HGF include induction of c-met mediated cell division in many epithelial and endothelial cells, including trophoblast and vascular endothelium.^{14 15} Motogenesis describes the “scattering” effect of

HGF on epithelial cell colonies in monolayer culture.²⁴ “Scattering” is best summarised as cell dissociation and migration—an effect observed in vitro on some (though not all) cells expressing c-met. Morphogenesis refers to the ability of HGF to induce tubular formations in several three dimensional cell culture models.¹⁵ This action seems unique to HGF and has not been observed among other growth factors.⁴

Hepatocyte growth factor has been shown to be cytotoxic or cytostatic to certain tumour cell lines including hepatocellular carcinoma, ovarian adenocarcinoma, and squamous carcinoma.²⁵ Conversely, HGF can also mediate the growth, invasion, and metastasis of various other human carcinoma cells in vitro.¹⁴ This is predominantly a paracrine phenomenon apparently mediated by stromal fibroblasts, although autocrine stimulation has been described in some tumour cells derived from human malignancies.

Hepatocyte growth factor also has considerable angiogenic potential because of its positive effects on endothelial cell growth and motility. Ingrowth of new blood vessels has been induced by HGF in mouse subcutaneous tissue and rat cornea, and HGF is detectable at sites of neovascularisation within human psoriatic plaques.²⁶ Other recent studies have shown that HGF has a role in such diverse events as pancreas and thyroid gland growth and function, chondrogenesis, and reticuloendothelial cell production, differentiation and activation (including haematopoiesis, T lymphocyte adhesion and migration, and B cell immunoglobulin secretion).^{14 15}

Important events during normal development are driven by mesenchymal/epithelial cell interaction: the localisation of HGF and c-met to these same cell types, combined with their known paracrine actions, suggests a possible role for them in such signal exchange.²⁷ Furthermore, the specific cellular effects of HGF described above could be particularly important in various mesenchymal/epithelial interactions known to occur during embryogenesis. For instance, in the development of both the embryonic lung and the meso- and metanephric kidneys, mesenchymal tissue is known to stimulate underlying epithelium to proliferate, invade, and organise itself into branching tubules. All these effects could be mediated by HGF, and Sonnenberg *et al* have localised HGF and c-met mRNA to mesenchymal and epithelial cells, respectively, within embryonic mouse renal and pulmonary tissue.⁴ The same group have also localised HGF/c-met messages in other embryonic mouse tissues where mesenchymal/epithelial interactions are thought to be important, including neural, dental, nasal and hepatic tissues, the tongue and major blood vessels.

HGF/c-met in embryogenesis

Three studies have now been published that describe the effect of disrupting the gene for either HGF or c-met on the embryogenesis of mice.^{5–7} The authors altered part of the genetic code to prevent HGF binding to its receptor. Mice heterozygous for the gene defect

(HGF+/- or *c-met* +/-) were produced and their litters studied. Normal homozygous (+/+), heterozygous (+/-) and abnormal homozygous (-/-) pups were produced in the expected Mendelian proportions (1:2:1) and only the abnormal homozygotes seemed adversely affected. None survived beyond embryological day (E) 17.5 (term is between E18 and E22) and clinically significant developmental abnormalities were found. In the absence of functional *c-met*, failure of migration of myogenic precursor cells into the tongue, limb buds and diaphragm and failure of normal placental and liver development were observed.⁶ When the gene for HGF was disrupted, observations were limited to abnormal liver and placental formation.^{5,7}

FETAL LIVER DEVELOPMENT

Transcripts for both HGF and *c-met* have been found in fetal liver, but the technique used did not identify the specific cell types involved.⁴ All of the gene "knock out" studies reported severe abnormalities of liver development in the functional absence of either HGF^{5,7} or *c-met*.⁶ A reduction in liver volume of 40% was noted at E12.5. By early third trimester (E14.5) the fetal livers were under half their normal weight and Schmidt *et al* reported major disruption of the normal architecture, which was most noticeable on the ventral aspect.⁵ Gross morphological abnormalities were observed, together with significantly depleted hepatocytes; these abnormalities were identical whether HGF or *c-met* was deleted—evidence of the unique nature of their interaction.

PLACENTAL DEVELOPMENT

Human placenta seems to be one of the richest sources of HGF,²⁸ which was first sequenced from a human placental cDNA library.¹⁶ Schmidt *et al* and Uehara *et al* demonstrated independently that HGF is essential for normal placentation in mice.^{5,7} Bladt *et al* showed that disruption of the *c-met* gene causes identical malplacentation.⁶ Aside from a substantial reduction in placental size, the key developmental abnormality observed was in the labyrinth region—homologous to the tertiary villi of the human placenta.

The labyrinth region normally consists of numerous fine embryonic vessels surrounded by trophoblast epithelial cells, which are bathed in maternal blood. The trophoblast cells within the placenta of the mutant embryos were significantly depleted, limiting the size of the labyrinth region. The network of embryonic vessels and maternal sinuses was also poorly developed, although the number of spongiotrophoblast cells in the junctional zone looked normal.

The first placental abnormalities were detected at E10.5, at about the time when the placenta begins to take over from the yolk sack as the embryo's main source of nutrients.²⁹ The homozygous mutant embryos all died between E13.5 and E17.5, and from their findings the authors attributed their demise to placental insufficiency, possibly in conjunction with the liver abnormalities described above.

The labyrinthine trophoblast cells are thought to derive from the extra embryonic ectoderm.³⁰ At E8, mitotic activity in the trophoblast cells is low, but by E10 it has increased substantially. This increased mitotic rate seems to coincide with the establishment of physical contact between the allantoic mesenchyme and the extra embryonic ectoderm around E8.5.³¹ It was suggested that the allantois may produce a paracrine growth factor to stimulate the ectoderm.

Uehara *et al* showed that normal (HGF +/+) allantoic cells have scattering activity that is consistent with the production of HGF, while the allantoic cells from the placenta of mutant (HGF-/-) embryos possess none.⁷ They also demonstrated the expression of *c-met* by the labyrinthine trophoblast cells (homologous to the cytotrophoblast cells of the human placenta) using immunohistochemistry. They then showed that trophoblast cells from the placenta of both normal (HGF+/+) and mutant (HGF-/-) embryos responded to HGF in vitro (increased growth rate).

This work supports the hypothesis that, at least in mice, the mesenchymal cells of the allantois produce HGF, which acts as a paracrine growth factor on the epithelially derived labyrinthine trophoblast cells, via *c-met*, to produce normal labyrinthine development. Absence of either HGF or *c-met* seems to prevent the normal growth and development of this region, leading to growth restriction and intrauterine death secondary to placental insufficiency.

Recent work sheds some light on the expression and distribution of both HGF and *c-met* in normal human placenta. Using in situ hybridisation techniques, HGF mRNA was strongly localised to the villous mesenchymal core and particularly the perivascular stroma and vascular smooth muscle.^{32,33} Substantial amounts of mRNA were also seen in the amnion and the chorion. The *c-met* transcript was found at low levels throughout the villous core, with a relatively high concentration at the (trophoblast derived) syncytio-/cytotrophoblast membrane.^{32,33} In contrast to HGF mRNA expression, *c-met* mRNA was not seen in either perivascular stroma or vascular smooth muscle.

Hepatocyte growth factor protein has been co-immunolocalised in the same areas as the *c-met* transcript, strongly staining villous trophoblast cells.^{32,33} Intense HGF immunoreactivity was found in the endothelial cells lining the villous vasculature and placental Hofbauer cells, as well as in the decidua of the basal plate. It was also found staining the amniotic epithelium, with a fainter signal from the chorion. This matches localisation of HGF mRNA in both amnion and chorion. *c-met* protein was found intensely staining the fused syncytio-/cytotrophoblast membrane and the vascular endothelium.

Horibe *et al* found no significant difference in the rate of production of HGF from placental tissue between first, second, and third trimester, but a steady rise in maternal serum levels to term.³⁴ This may reflect secretion of HGF from the placenta into the maternal

blood, with increasing placental mass through gestation leading to increasing serum concentrations. After birth maternal serum concentrations dropped to pre-pregnancy values within three days. Interestingly, the concentrations of HGF in cord blood (presumably venous, though not specified) at delivery were much lower than those in maternal serum, possibly indicating preferential release into the maternal vascular compartment.

Concentrations of HGF in the amniotic fluid were highest between 20 and 29 weeks of gestation, and amnion from the second trimester was shown to secrete 100-fold more HGF than that from the third trimester.³⁴ In contrast, other cytokines present in amniotic fluid (epidermal growth factor, tumour necrosis factor, interleukin-1, interleukin-6) increase in concentration towards term. As *c-met* transcripts are known to be present in the fetal lung, this unusual expression pattern in amniotic fluid may indicate a specific role for HGF in fetal pulmonary development.⁴

INTRAUTERINE GROWTH RESTRICTION

Severe IUGR is associated with characteristic pathological placental findings and reduced hepatic size, including hemilateral liver degeneration.³⁵ Placentae from pregnancies complicated by severe IUGR and absent umbilical artery end-diastolic blood flow ("placental insufficiency") are typically small in size. They display "persisting immaturity," a deficiency of terminal villi, and a reduction in villous trophoblasts. Reduced cytotrophoblastic proliferation leads to syncytiotrophoblast abnormalities due to reduced regeneration from the cytotrophoblast.¹⁰ This is not dissimilar to the small placenta with poorly developed labyrinthine region and reduced trophoblastic cell mass reported in mice with dysfunctional HGF or *c-met*.⁵⁻⁷ These embryonic mice also had small degenerative livers.

As described before, HGF and *c-met* (protein and mRNA) are expressed in normal human placenta. Furthermore, it has been shown that human cytotrophoblasts increase DNA synthesis in a dose dependent manner in response to HGF.³²⁻³³ One may therefore postulate that HGF, secreted by mesenchymal cells within the human placenta, is responsible for promoting normal villous development by its actions on the cytotrophoblast and the vascular endothelium, through binding with *c-met*.

Deficient trophoblast proliferation, differentiation, and invasion combined with inadequate angiogenesis is consistent with the observed findings in both the mouse gene "knock out" studies and in human placenta from severely growth retarded pregnancies associated with placental insufficiency. That in humans this may also be due to an abnormality of the HGF/*c-met* system is an attractive hypothesis presently under investigation at several centres including our own. We have already shown that expression of HGF and *c-met* is reduced within placentae from IUGR pregnancies using immunohistochemistry.³⁶

Conclusions

Specific expression of growth factors, such as HGF, are increasingly implicated in the regulation of placental growth and function, and thereby fetal growth and development. The spatial distribution of HGF and *c-met* within the human placenta suggests potential physiological actions, including angiogenesis and trophoblast growth. As such functions are important in placental development and consequently fetal wellbeing, it remains to be determined whether inappropriate expression of this glycoprotein or its receptor might lead to pregnancy complications such as IUGR.

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