Endocrinology of Growth

Ron G. Rosenfeld

Oregon Health and Science University, Portland, OR, USA

Abstract

Growth is a remarkably complex biological phenomenon, requiring the coordinated production of multiple hormones and growth factors. Human growth is characterized by several distinct features, including: (1) rapid growth in late gestation; (2) growth deceleration immediately following birth; (3) a prolonged childhood and a mid-childhood growth spurt; (4) a pubertal growth spurt; (5) relatively late attainment of adult height, and (6) minimal sexual dimorphism of adult stature. Secular changes in the height of humans probably reflect nutritional and environmental factors, rather than major genomic changes. While multiple hormones impact growth, the growth hormone (GH)-insulin-like growth factor (IGF) axis plays a central role in both intrauterine and postnatal growth. GH, after being secreted by the pituitary, binds to a transmembrane receptor and activates a postreceptor signaling cascade, ultimately leading to phosphorylation of signal transducer and activator of transcription (STAT) 5b. STAT5b transcriptionally regulates the genes for IGF-I and for key IGF-binding proteins. IGF-I, in turn, binds to the type 1 IGF receptor, resulting in chondrocyte proliferation and statural growth. IGF-deficient states may be divided into secondary forms, reflecting defects in GH production, and primary forms. Molecular defects of the GH-IGF axis have been identified in humans, with phenotypes that correspond to the specific genetic lesions. Therapy with GH or IGF-I can now be matched to specific defects in the GH-IGF axis.

Why Do Animals Grow?

Mammalian growth is an extraordinarily complex biological process. The difference in size between mycoplasma (10^-13 g) and the blue whale (10^8 g = 100,000 kg) is approximately 20 orders of magnitude, and yet both species presumably evolved from simple unicellular ancestors. One must infer from this observation that a wide variety of selective pressures directed the growth of each organism over evolutionary time, and that multiple genes and gene
products combined to organize and direct the panoply of growth patterns that characterizes life on earth.

We may begin by asking the fundamental question: Why do organisms grow? Why invest so much genetic and ultimately metabolic energy in a growth process, when there may be more urgent needs of an organism? Much of this is dictated, of course, by the simple fact that animals are born small and, generally, helpless. Growth is required to achieve sizes necessary to fulfill the animal's adult functions of gathering, predation, defense, socializing and reproducing. Different societal structures dictate different growth patterns: in gorillas, where the dominant adult male controls a harem, the male gorilla is often twice the size of his female partners; in humans, the adult height differential between adult males and females is only 7%, reflecting the generally monogamous nature of human society [1]. A more detailed view of the lifespan of human growth pattern demonstrates some additional interesting and unique features that discriminate human growth from that of other mammals, including primates [2]:

1. Maximal growth occurs during gestation
2. The normal time of gestations for humans is relatively short relative to their body size
3. Growth decelerates immediately following birth
4. Relatively late sexual maturation
5. Puberty commences at a time when the growth rate is slowest in all of childhood
6. The presence of a distinct pubertal growth spurt in height
7. Delay between puberty and full reproductive capacity

Anthropologists and auxologists have debated the selective forces which have shaped human growth patterns. It has been proposed that a relatively short gestation is required to allow accommodation of a relatively large brain/head through the birth canal. A prolonged childhood with a relatively modest growth rate promotes an infantile appearance, which would foster the transmission of knowledge and culture from one generation to the next, as well as prevent juvenile males from presenting a competitive sexual threat to adult males. A rapid and pronounced pubertal growth spurt would then allow adolescents to rapidly attain ideal adult heights at a delayed age. The relative lack of sexually dimorphic growth in human males and females (the 7% difference in adult height is largely explained by different pubertal growth patterns in earlier epiphyseal fusion in females), allows for an adult female size that can accommodate the carrying and delivery of a human fetus and newborn; adequate pelvic size is necessary to not only support the size of the fetus, but to permit delivery of the relatively large fetal cranium characteristic of Homo sapiens.

As one considers the remarkable complexity of mammalian growth, it becomes apparent that regulation must occur on multiple, carefully integrated levels. Only a robust system of interacting hormones and growth factors
could possibly allow the multiple stages of growth characteristic of complex mammals, as well as the intricate coordination with metabolic and reproductive needs. To attempt to explain growth of mammals in terms of one or two hormones is ludicrously reductive and fails to do justice to the remarkable interspecies differences, as well as the complexity of growth within individual species. Nevertheless, as explained below, decades of investigations have suggested that the growth hormone (GH)-insulin-like growth factor (IGF) axis plays a predominant role in both intrauterine and postnatal growth [3].

**What Causes Animals to Grow?**

Attainment of the complex growth pattern described above requires the interaction of multiple hormones and growth factors, which must be generated in a timely fashion relative to the life cycle and which, in general, interact with one another, rather than working in isolation. Despite this complexity, over the last 50 years, it has become increasingly apparent that the IGFs play a central role in both intrauterine and postnatal growth. The original observation by Salmon and Daughaday [4] in 1957 showed that: (1) the addition of normal serum to rat cartilage stimulated the incorporation of radioactive inorganic sulfate into acid mucopolysaccharides; (2) serum from hypophysectomized rats could not duplicate this effect, unless the rats had first been treated in vivo with GH; and (3) addition of GH, itself, to the cartilage medium could not stimulate sulfate incorporation. In subsequent studies, this GH-stimulated factor(s) was also found to enhance the incorporation of leucine into protein-polysaccharide complexes, uridine into RNA and thymidine into DNA [5]. The authors concluded that GH, while not able to directly mediate cellular growth, itself, must stimulate the production of a ‘sulfation factor’, which then enhanced chondrocyte growth and metabolism.

By 1972, proteins which had been initially designated sulfation factor, multiplication-stimulating activity, and nonsuppressible insulin-like activity were found to be related and were renamed ‘somatomedins’ [6]. With the elucidation of the amino acid sequences of two of these proteins and discovery of their close structural relationship to insulin, the term somatomedin was replaced by IGF-I and -II [7].

**IGF Structure**

IGF-I is a basic peptide of 70 amino acids, while IGF-II is a slightly acidic peptide of 67 amino acids [7]. The two peptides share 45 of 73 possible amino acid positions, and have approximately 50% amino acid homology to insulin. Like insulin, both IGFs have A and B chains connected by disulfide bonds. The connecting C-peptide region is 12 amino acids long for IGF-I and 8 amino
acids for IGF-II; neither IGF C-peptide bears any homology with the C-peptide region of proinsulin. IGF-I and -II also differ from proinsulin in possessing carboxy-terminal extensions, or D-peptides, of 8 and 6 amino acids, respectively. This structural similarity explains the ability of both IGFs to bind to the insulin receptor and of insulin to bind to the type I IGF receptor, thereby explaining the ‘insulin-like’ activity of the IGFs, as well as the growth-promoting ability of insulin. Structural differences between insulin and the IGFs, on the other hand, probably also explain the failure of insulin to bind with high affinity to the IGF-binding proteins (IGFBPs).

GH appears to be the primary regulator of IGF-I gene transcription, which begins as early as 30 min after intraperitoneal injection of GH into hypophysectomized rats. It is critical to note, however, that IGF production in utero is essentially GH independent, and that GH regulation of IGF-I synthesis does not appear to become a factor until very late gestation, at the earliest. Thus, children with congenital GH deficiency or GH insensitivity are essentially normal size at birth. The factors that regulate IGF-I synthesis in the fetus remain to be elucidated, but it is likely that placental viability, fetal nutrition and insulin production all play roles.

As discussed in more detail below, it now appears that signal transducer and activator of transcription (STAT) 5b is the most critical mediator of GH-induced activation of IGF-I gene transcription, an observation underscored by studies involving target disruption of the STAT5b gene in mouse models [8] and by the reports of patients with severe GH insensitivity associated with homozygosity for mutations of the STAT5b gene [9, 10]. Two adjacent STAT5 binding sites have been identified in the second intron of the rat IGF-I gene, within a region previously identified as undergoing acute changes in chromatin structure after GH treatment [11].

The factors involved in the regulation of IGF-II gene expression are less clear and, indeed, the role of IGF-II is still uncertain, especially postnatally. As discussed below, knockout studies have confirmed the importance of IGF-II in fetal growth, but its role in postnatal life is far less clear. In humans and rats, IGF-II gene expression is high in fetal life, having been detected as early as the blastocyst stage in mice. In general, fetal tissues have high IGF-II mRNA levels that decline postnatally, although brain IGF-II mRNA remains high in the adult rat.

Targeted Disruption of the IGF Genes

Our understanding of the role of the IGF axis in fetal and postnatal growth was strongly supported by a series of studies involving IGF and IGF receptor null mutations [12]. Previous studies had shown that knockouts of either GH or the GH receptor genes resulted in little change in birth size, confirming the minimal role of GH in fetal growth. On the other hand, mice with knockouts of
the gene for either IGF-I or IGF-II were found to have birthweights approximately 60% of normal. Mouse mutants lacking both IGF-I and the GH receptor are only 17% of normal size. These observations and others indicated that: (1) both IGF-I and IGF-II are important embryonic and fetal growth factors; (2) IGF-I plays a critical role in postnatal growth; and (3) GH, itself, does have some modest, apparently IGF-independent role as well. Growth delay began on day e11 for IGF-II knockouts and on day e13.5 for IGF-I knockouts. Those mice with IGF-I gene disruptions who survived the immediate neonatal period continued to have growth failure postnatally, with weights 30% of normal by 2 months of age. Indeed, postnatal growth was poorer than that observed in mice with GH-R, GHRH receptor mutations or pit-1 mutations, indicating that both GH-dependent and GH-independent factors are necessary for normal growth. When the genes for both IGF-I and IGF-II were disrupted, weight at birth was only 30% of normal, and all animals died shortly after birth, apparently from respiratory insufficiency secondary to muscular hypoplasia.

These experimental observations in mice have been paralleled by human mutational analysis. It had, for example, long been known that children with GH gene deletions or with mutations or deletions of the GH receptor gene were near normal size at birth, but had severe postnatal growth retardation [13, 14]. When the first case of a human IGF-I gene deletion was reported, the patient was found to exhibit a prenatal and postnatal growth pattern similar to that observed in the mouse knockouts [15], and this was further confirmed in a more recent report of a bioinactive IGF-I molecule, resulting from a missense mutation [16].

Challenges to the fundamental model of the IGF system resulted from studies employing specific ablation of hepatic IGF-I production through the Cre/loxP recombination system [17]. These investigations confirmed that the liver is the principal source of circulating IGF-I, but also demonstrated that an 80% lowering of serum IGF-I levels had no apparent effect on postnatal growth, thereby suggesting that postnatal growth was relatively independent of hepatic IGF-I production. One must presume, consequently, that either local (paracrine) chondrocyte production of IGF-I or other tissues (??adipose) was sufficient to maintain adequate production of IGF-I to account for growth preservation, or, alternatively, that free IGF-I levels remained within the normal range as a result of the reciprocal increase in GH production, as well as the lowering of serum IGFBPs. Supportive data for the predominant role in growth of locally produced IGF-I are the only modest decrement of postnatal growth seen in acid-labile subunit (ALS, part of the IGFBP system) null mice [18].

In subsequent studies involving the crossing of liver-derived IGF-I gene-deleted mice (LID) with ALS gene-deleted mice (ALSKO), an 85–90% reduction in serum IGF-I was achieved, and, in this case, early postnatal growth retardation was observed [19]. These findings suggest that postnatal growth is dependent upon both endocrine (i.e. hepatic) and tissue IGF-I, although definite conclusions are problematic in the face of the elevated GH produc-
tion and perturbations of the IGFBP system observed in these studies. What seems most likely, when the totality of these studies is evaluated, is that both endocrine and autocrine/paracrine IGF plays a role in growth [20, 21].

Knockout of the gene for the type 1 IGF receptor resulted in birthweights 45% of normal and 100% neonatal lethality. Abduzzahab et al. [22] have reported 2 patients with intrauterine growth retardation and postnatal growth failure, despite elevated serum IGF-I concentrations. One patient was a compound heterozygote for point mutations in exon 2 of the IGF-1R gene, leading to decreased receptor affinity for IGF-I, while the second had a nonsense mutation of one allele, resulting in reduced numbers of IGF-1 receptors. More recently, fetal and postnatal growth retardation have been observed in a number of patients heterozygous for one mutation of the IGF1R gene. In mice, concurrent knockout of genes for IGF-I and the type 1 IGF receptor resulted in no further reduction in birth size (45% of normal), consistent with the concept that all IGF-I actions in fetal life are mediated through this receptor. On the other hand, simultaneous knockout of the genes for IGF-II and the type 1 IGF receptor resulted in further reduction of birth size to 30% of normal (as with simultaneous knockouts of IGF-I and IGF-II); this raises the possibility that some of the fetal anabolic actions of IGF-II are mediated by a secondary mechanism (perhaps, placental growth or IGF-II interactions with the insulin receptor). Whatever the pathway may prove to be, it does not appear to involve the type 2 IGF receptor, since knockout of this paternally imprinted gene results in an increased birthweight, but death in late gestation or at birth. Since this receptor normally degrades IGF-II, increased growth presumably reflects excess IGF-II acting through the IGF-I receptor.

Several conclusions can be drawn from these studies: (1) IGF-I plays a critical role in both fetal and postnatal growth; (2) IGF-II is a major fetal growth factor, but has little, if any, role in postnatal growth; (3) the type 1 IGF receptor mediates anabolic actions of both IGF-I and IGF-II; (4) the type 2 IGF receptor is bifunctional, serving to both target lysosomal enzymes and to enhance IGF-II turnover; (5) IGF-I production is involved in normal fertility; (6) placental growth is only impaired with IGF-II knockouts; (7) GH and the GHR play little role in prenatal growth; (8) IGF-I is the major mediator of GH’s effects on postnatal growth, although GH and the GHR may have a small IGF-independent effect. Whether these studies in mice are fully applicable to humans is yet unknown, although much has been learned in recent years from rare cases of human mutations of critical genes of the GH-IGF axis.

**GH Receptor**

The coding and 3′-untranslated regions of the human GH-R are encoded by nine exons, numbered 2–10 [23]. Exons 3–7 encode the extracellular, GH-binding domain. Examination of the crystal structure of the GH-GH-R
complex revealed that the complex consisted of one molecule of GH bound to two GH-R molecules, initially suggesting that GH induced receptor dimerization as a necessary step in its action. Recent studies, however, have indicated that the receptor may be constitutively dimerized, and that receptor activation involves a GH-induced conformational change [24].

Although it was originally suspected that the GH receptor might be capable of autophosphorylation, it is now apparent that the GHR must recruit a cytoplasmic tyrosine kinase, as the receptor, itself, lacks intrinsic kinase activity. JAK2 (Janus kinase 2) has been identified as the critical GH receptor-associated tyrosine kinase; loss of ability of the GHR to bind JAK2 results in loss of GH-induced GHR signaling. Recruitment and/or activation of JAK2 molecules by the GHR promotes their enzymatic activity via cross-phosphorylation, and the active kinases then phosphorylate tyrosines on the intracellular portion of the GHR, itself, thereby providing docking sites for critical intermediary proteins, such as the STATs (signal transducers and activators of transcription). There are seven known mammalian STATs; of these, STAT5b appears to be most centrally involved in mediating the growth-promoting actions of the GHR, as indicated by several gene disruption studies in rodent models [8]. The reports of the seven cases of homozygous human STAT5b mutations, presenting with severe growth failure and GH resistance, have further substantiated the critical intermediary role of STAT5b in GH regulation of IGF-I gene transcription and growth [9, 10]. The STAT proteins dock, via their src-homology-2 (SH2) domain, to phosphotyrosines on ligand-activated receptors, such as the GHR, and are subsequently phosphorylated on single tyrosines at the C-terminus of the protein, dimerize, translocate to the nucleus, bind to DNA through their DNA-binding domain, and in turn regulate gene transcription.

IGF Deficiency

Given the central role of the IGF system in both intrauterine and postnatal growth, assessment of patients with otherwise unexplained growth failure requires an evaluation of the IGF axis [25]. By analogy with other endocrine systems, IGF deficiency (IGFD) has been divided into secondary etiologies (i.e. IGFD resulting from disorders of GH production, at either the hypothalamic or the pituitary level) and primary forms (i.e. IGFD despite normal GH production). Primary IGFD was first identified in the 1960s in patients who ultimately proved to have GH insensitivity resulting from mutations or deletions of the GH receptor gene [14]. Over the last decade, however, multiple other molecular etiologies (table 1) have been identified, including defects in the post-GH receptor signaling cascade (STAT5b) [9, 10], mutations and deletions of the IGF-I gene [15, 16], mutations in genes encoding IGFBPs [26, 27], and mutations in genes for the IGF-I receptor (the latter actually represents a form of IGF resistance) [22]. Molecular analysis of such patients has proven to be invaluable,
Table 1. Molecular defects resulting in primary IGFD

<table>
<thead>
<tr>
<th>GH receptor abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations/deletions of GHR affecting the extracellular domain of the GH receptor and resulting in decreased GH binding</td>
</tr>
<tr>
<td>Mutations/deletions of GHR affecting the ability of the GHR to dimerize</td>
</tr>
<tr>
<td>Mutations/deletions of GHR affecting the transmembrane domain of the receptor and resulting in defective anchoring in the cell membrane</td>
</tr>
<tr>
<td>Mutations/deletions of GHR affecting the intracellular domain and signaling</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-GHR signaling defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations of STAT5b resulting in defective or absent GH signal transduction</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mutations/deletions of IGF-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deletions of IGF-1</td>
</tr>
<tr>
<td>Mutations of IGF-1 resulting in bioinactive IGF-1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Defects of IGF-1 transport and/or clearance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations/deletions of ALSIGF, resulting in defective IGF-1 transport and rapid IGF-1 clearance</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>IGF-1 resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mutations of IGF1R, resulting in decreased sensitivity to IGF-1</td>
</tr>
</tbody>
</table>

as specific genotypes predict specific phenotypes. For example, patients with primary IGFD resulting from defects of the GH receptor or STAT5b genes have normal birth size, but severe postnatal growth failure, while patients with IGF-I gene defects also have intrauterine growth retardation, microcephaly, developmental delay, and variable hearing deficits. These features reflect the relative roles of GH and IGF-I in prenatal and postnatal growth.

**Therapeutic Implications**

For decades, therapy for growth disorders was dominated by GH, first a human cadaver-derived form and then, beginning in the mid 1980s, in a recombinant DNA-derived form. GH remains the treatment of choice for patients with secondary IGFD, as daily dosing allows replacement of deficient pituitary production of GH and adequately stimulates IGF-I synthesis. The market for GH has greatly expanded, however, to include a wide variety of disorders characterized by short stature, but normal GH production, including such conditions as Turner syndrome, chronic renal failure, Noonan syndrome, small for gestational age infants with failed catch-up growth, and a heterogeneous group of conditions lumped under the heading of ‘idiopathic short stature’. In general, children with these conditions do appear to respond to pharmacological dosages of GH, although growth acceleration generally is not as good as in replacement therapy of GH deficiency.
IGF-I therapy for patients with primary IGFD was first tested in the 1990s, primarily in patients with GH receptor defects. Growth acceleration was observed and sustained in most of these patients, although, in general, the growth response was not quite as good as observed in patients receiving GH replacement therapy for GH deficiency. The total explanation for this discrepancy remains unclear, but probably involves the failure of systemic IGF-I administration to fully replace local IGF production, especially at the epiphyseal growth plates. Nevertheless, IGF-I remains the treatment of choice for patients with defects at the level of the GH receptor, the JAK-STAT system and the IGF-I gene [28].

Both the FDA and the European authorities have now approved IGF-I therapy for treatment of children with short stature and ‘severe primary IGFD’, defined as a height below –3 SD, normal GH, and a serum IGF-I below –3 SD (USA) or below –2.5 percentile (Europe). Clinical trials will be necessary to determine whether optimal treatment for such patients and, especially, for less severe forms of IGFD, should be with GH, IGF-I, or, possibly, a combination of GH plus IGF-I.

References


**Discussion**

**Dr. Gillman:** Two questions, what's known about IGF-II in the human, both pre-natal and postnatal growth; the second question is you have talked a lot about genetic determinants of linear growth, what about epigenetic determinants?

**Dr. Rosenfeld:** Actually, you can combine both of those questions in a sense, as you probably know. IGF-II is a mystery. We know from animal knockout studies that it is involved in rodent fetal growth, it's not involved in rodent postnatal growth. There are to date no published reports of IGF-II mutations or gene deletions, but IGF-II is an imprinted gene and the expression depends upon various methylation processes. There is now a growing body of literature to suggest that variation in methylation of IGF-II can be responsible for much of intrauterine growth retardation. There are a number of studies primarily from France now that suggest that what people might have called Silver-Russell dwarfism or some variation of intrauterine growth retardation may be explained in about 70% of cases by variations in methylation of IGF-II. So I think we should be paying more and more attention to IGF-II and to epigenetic processes that regulate IGF-II gene expression as determinants of fetal growth. In terms of epigenetics of IGF-I, to some extent we have been discussing this over the last few days. We have heard yesterday and today about variations in serum IGF-I levels dependent upon breastfeeding versus formula feeding. Probably a simplistic way one
might say that various dietary compositions are going to epigenetically regulate IGF-I gene expression and that may be one of the mechanisms by which different formulas or breastfeeding impact neonatal growth. So I think that’s a critical question, thank you for mentioning it.

Dr. Domellöf: As a neonatologist, I am interested in small preterms. We know that they have postnatal growth failure, we know that they have low IGF-I concentrations and we know that IGF-I is responsive to protein supply. Is there anything more known about nongrowth hormone factors promoting IGF-I secretion?

Dr. Rosenfeld: Growth hormone as I mentioned must bind to its transmembrane receptor. It has multiple signaling pathways once it binds to the receptor including MAP kinase, etc. It’s believed that the JAK-STAT, STAT5b pathway is the major if not the only pathway through which growth hormone regulates IGF-I, but the other pathways distal to the growth hormone receptor are probably responsible for many of the metabolic actions of growth hormone. In my simplistic model, growth hormone binds to the receptor, activates the JAK STAT system which activates IGF-I but also activates other pathways which are responsible for the lipolytic diabetogenic roles of growth hormone. It may well be that one of the reasons why we see growth failure in patients with severe nutritional deprivation is that there is an uncoupling of this pathway. For example, children with severe malnutrition typically have very low IGF-I levels, whereas growth hormone levels may be normal or even increased presumably because of this uncoupling.

Dr. Domellöf: But if we regard growth in these extremely preterm infants as similar to fetal growth, which is not regulated by growth hormone, it must be regulated by some other factors that influence IGF-I.

Dr. Rosenfeld: You are asking what regulates IGF-I in utero? Is that the question? I wish I knew. It’s probably not a pituitary hormone, it probably is directly related to fetal nutrition and placental sufficiency; whether it’s a direct effect of fetal nutrition on IGF or perhaps mediated by fetal insulin production in utero as a response to nutrition, that’s not known. The other interesting question is what is it at birth that suddenly turns on growth hormone dependency of IGF, that’s also not known. So those are both very interesting questions in which research needs to be done.

Dr. Batubara: Is it true that IGF-II is more important than IGF-I prenatally? And the second question, when do we begin to suspect a gene defect in children with growth failure?

Dr. Rosenfeld: When we first started doing this, not very many years ago, we really only analyzed children with very severe growth failure, –4, –5, –6 standard deviations. But as we gained more experience, we began to appreciate that we could find genetic molecular abnormalities in children with milder height defects. It’s hard for me therefore to give you a simple answer. I would say that if you have an extremely strong family history of growth failure over multiple generations, that is suggestive. Or if you have a family where everybody has a normal stature and this one child stands out from everybody else, that also is suggestive. If we measure IGF-I and the IGF-I level is very low, that is suggestive to us. Unfortunately, I don’t have any firm rules to say this is a child that requires evaluation, this is a child that does not; we are really just beginning to appreciate it. Certainly the shorter the child, the lower the IGF-I, the more likely we are to find a molecular defect in the growth hormone IGF axis, but there is no clear dividing line.

Dr. Batubara: What about the role of IGF-I prenatally?

Dr. Rosenfeld: In utero it appears that both IGF-I and IGF-II are essential; postnatally, probably just IGF-I.

Dr. Sutomo: I am very interested in the analysis of the gene responsible for growth failure. Which is the most common one that you found in your cases?
Dr. Rosenfeld: The growth hormone receptor gene by far, over 300 cases now in the world, and really all over the world there are in fact several cases, in Malaysia as well.

Dr. Sutomo: Has a specific mutation been found in that gene?

Dr. Rosenfeld: It has been found. It was originally reported in the Mediterranean region, actually originally in Israel, but we now know that these mutations are found all over the world. They're particularly prevalent in inbred populations as is often the case for autosomal recessive disorders. You should suspect it if you have a child who has a normal size at birth, severe postnatal growth failure, very low IGF-I with normal or elevated growth hormone. If you see that, then you should be suspicious of that possibility.

Dr. Hüppi: I have a question regarding the preterm infant and the abnormalities in brain development that might be related to changes in IGF. Do you have data that show to what extent the preterm infant switches to the growth hormone-inducing IGF immediately after birth or postconceptionally?

Dr. Rosenfeld: As far as I can tell there are no definitive data. The suggestion is that actually growth hormone dependency begins immediately before birth rather than right after birth, but I am not sure how firm those data are. The developmental abnormalities have not been seen in patients with growth hormone deficiency or growth hormone receptor deficiency. They have been seen in patients with IGF-I gene defects or IGF-I receptor defects, suggesting that IGF in a growth hormone-independent manner is responsible for some neural development in utero.

Dr. Hüppi: To what extent is the phenotypic expression of mental retardation linked to the gene product? Do you see mental retardation more in a homozygous or mixed heterozygous expression?

Dr. Rosenfeld: The three IGF-I cases that have been studied were all homozygous, and they were the ones with the most severe neurological handicap. The IGF-I receptor defects, as I mentioned, were all heterozygous except for one case that was a mild compound heterozygous. They have milder neurological impairment, so it probably is a quantitative process.

Dr. Lucas: About 50 human studies and quite a large number of animal experiments now show that rapid early growth programs long-term cardiovascular disease and obesity risk, and there is a search for the coupling mechanism that links this early growth event to its long-term effects. IGF-I has been reported to be potentially part of that coupling mechanism, also potentially for cancer as well. You may feel this is sort of outside your brief here, but as someone interested in IGF-I do you have any views on how this can actually operate?

Dr. Rosenfeld: I think it’s a very important question, obviously it’s an area of very active research. We know from multiple different animal models that mice and rats that are congenitally growth hormone deficient or have congenital IGF deficiency or IGF receptor deficiency live longer, and we are talking about 25–30% longer, so it’s not a trivial difference. It has been suggested that perhaps a unifying mechanism for the Barker hypothesis is that whatever the ideology of it is, whether it’s the combination of intrauterine growth retardation and rapid postnatal growth, IGF is the linchpin. Perhaps given the setting of intrauterine growth retardation, overfeeding, rapid growth in early life, you turn on the IGF-I gene expression overabundantly and that then leads to long-term metabolic consequences as part of the Barker hypothesis. To complicate the matter even further, as you suggested, there are epidemiological data to suggest that humans who have IGF-I levels in the upper part of the normal range have a 2- to 3-fold greater incidence of certain cancers such as prostate cancer, premenopausal breast cancer, colon cancer than the individuals who have IGF-I levels in the lower part of the normal range. Not all studies find this, it’s still a controversial
area, but as you suggested there is great interest in the possibility that IGF-I is implicated in both long-term metabolic disease on the one hand and cancer on the other, so obviously an important area.

Dr. Moelgaard: We have just published data on IGF-I levels in children at 9 months in relation to their IGF-I levels at 17 years, and there is a clear inverse relation. The highest levels are found early and the lowest when they are 17.

Dr. Rosenfeld: That’s very interesting. There are even data from Sweden to suggest that taller people have higher IGF-I levels and have a higher risk of cancer than shorter people with lower IGF-I. On the other hand, there are also epidemiological data to suggest that low IGF-I is associated with cerebrovascular disease so I think the bottom line is you are going to die of something whether your IGF-I is low or high.

Dr. Gillman: Can I follow up on Alan’s question because I am totally confused now. First of all, can you distinguish between linear growth and adiposity with regard to IGF-I because my preconceived notion is that there is early growth in infancy that’s related to later obesity and cardiovascular disease, that is growth in adiposity rather than linear growth, maybe that’s not true. Secondly, what about the components of linear growth, specifically leg length, long bones vs. trunk, because even though taller stature is related to blood pressure specifically, especially in kids, leg length is inversely related to blood pressure, so IGF, linear growth, adiposity, components of linear growth, put it all together please.

Dr. Rosenfeld: I think those are very important reservations and of course we all know that association is not the same thing as causality and so it becomes very complicated in situations like this to know whether changes in IGF levels are just innocent bystanders or cause and effectors, I agree.