CMLS, Cell. Mol. Life Sci. 54 (1998) 1083–1094
1420-682X/98/101083-12 $ 1.50 + 0.20/0

CMLS Cellular and Molecular Life Sciences

The role of growth hormone and insulin-like growth factors in the immune system

S. C. van Buul-Offers[a,*] and R. Kooijman[b]

[a]Wilhelmina Children's Hospital, Department of Endocrinology, Postbus 18009, NL-3501 CA Utrecht (The Netherlands), Fax +30 2334825, e-mail: S.vanBuul@wkz.azu.nl
[b]Department of Pharmacology, Free University of Brussels, Medical School, Laarbeeklaan 103, B-1090 Brussels (Belgium)

Abstract. Growth hormone (GH) and insulin-like growth factor I (IGF-I) can modulate the development and function of the immune system. In this chapter, we present data on the expression of receptors for GH and IGFs and the in vitro and in vivo effects of these proteins. We show that expression of GH and IGFs in the immune system opens up the possibility that these proteins are not only involved in endocrine control of the immune system but can also play a role as local growth and differentiation factors (cytokines). Endocrine control of GH could be direct or mediated via endocrine or autocrine/paracrine IGF-I. In addition, GH can act as an autocrine or paracrine factor itself. Furthermore, IGF-I in the immune system has been shown to be regulated by cytokines, such as interleukin-1 and interferon-γ, alluding to a cytokine-like function of IGF-I. In addition to data on the function of GH and IGF-I in the immune system, we present new findings which imply a possible function of IGF-II and IGF-binding proteins.

Key words. Growth hormone; insulin-like-growth factor-I and -II; immune system; transgenic mice; insulin-like growth factor-binding proteins.

Introduction

Pituitary hormones and the insulin-like growth factors (IGFs) are prominent participants in the orchestration of growth and development. They either cooperate or compete with other growth factors, such as epidermal growth factor (EGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor α and β (TGFs), and nerve growth factor (NGF), in passing cells through the cell cycle. Consequently, this can lead either to growth stimulation or inhibition, as well as to differentiation, preservation, apoptosis, tumorigenesis and so on. It is therefore evident that these growth factors and hormones are involved in different processes, the functioning of the immune system being only one example. Readers are referred to several recent reviews on different aspects of the role of growth hormone (GH), prolactin (Prl) and the IGFs in the immune system [1–4]. Here we will mainly focus on the physiological role of GH, the insulin-like growth factors I and II, and their binding proteins in the immune system.

* Corresponding author.

The GH-IGF system of ligands, receptors, binding proteins, proteases and protease inhibitors

GH, GH-receptor and GH-binding protein

GH, occurring in serum as polypeptides of 20 and 22 kDa, is mainly produced by the pituitary [5]. GH

synthesis and secretion are mainly regulated by the pituitary transcription factor Pit-1 as well as by hypothalamic factors such as GH-releasing hormone and somatostatin [6]. Pit-1 is important for the differentiation and maintainance of the GH- and PRL-producing cells in the pituitary [7, 8] and the regulation of hormone secretion. GH exerts its effects through the GH receptor, which itself is a monomeric transmembrane molecule, and GH-induced receptor dimerization is required for signal transduction mediated mainly by the JAK-STAT proteins [9–12]. GH receptors are present in many tissues, (i.e the liver). Numerous mutations of GH receptors have been reported, which are localized in the extracellulair domain, and only a few in the intracellular domain [13].

The extracellular domain of the GH receptor can be proteolytically split off and is present in the circulation (GH-binding protein, GHBP), where it competes with membrane receptors for the available GH. GHBP binds GH with a high affinity, and it has been suggested that circulating GHBP levels modulate GH receptor effects [14, 15].

The expression of GH and its receptor in cells of the immune system suggests that GH may act both in an endocrine and paracrine/autocrine way, and it indicates an interplay between the immune and endocrine systems.

IGF-I and IGF-II

In most cases GH action is mediated by the IGFs, although direct actions may exist as well, as reported by several authors [16, 17]. The IGFs, polypeptides of approximately 7 kDa, are mainly produced by the liver under the influence of GH. In contrast, the regulation of expression of IGF-I and IGF-II, as in many other tissues, can be completely independent of GH. IGF-I levels in blood in particular can be used as a marker for GH deficiency (GHD), caused either by lack of GH, a biologically inactive GH molecule, or by defective GH receptors or post-receptor signalling in the case of GH-insensitivity syndrome [18].

Receptors for the IGFs

The IGFs can interact with several receptors, such as the insulin receptor, the type I IGF receptor, the type II IGF receptor and hybrid receptors; the latter consist of part of the insulin receptor and part of the type I IGF receptor. All these receptors are expressed by many tissues. The insulin receptor and type I IGF receptor consist each of two α and two β chains, linked together by S-S bridges.

The insulin receptor mediates most of the metabolic actions of both insulin and the IGFs, although there is evidence for a growth-promoting function as well [19]. After interaction of the ligands with either the insulin receptor or the type I IGF receptor, the receptor will become activated by autophosphorylation. The ensuing signalling is characterized by a series of phosphorylation reactions and specific interactions between intracellular molecules [20, 21].

In general, the type I IGF receptor is the most important mediator for the effects of IGFs on mitogenesis, apoptosis, cell motility, tumorigenesis and metastasis [22–24]. Overexpression of the type I IGF receptor induces transformation, and activation blocks programmed cell death (apoptosis) [25]. Distinct sites within the intracellulair domain of the type I IGF receptor are responsible for tumorigenesis and metastasis [22]. Transcription of the type I IGF receptor gene is upregulated by PDGF and bFGF. This results in enhanced cell cycle progression [22].

Peripheral blood lymphocytes are used by many investigators to determine numbers and affinities of receptors in conditions of impaired growth or other diseases [26]. The possible use of lymphoblast cell lines from African Pygmies in the diagnosis of abnormalities in the IGF system has been reported. These cells were found to have decreased type I IGF-receptor expression [27], which can partly explain the growth retardation of these individuals.

The biological function of insulin/IGF-I hybrid receptors is still unknown. In general they act as classical type I IGF receptors. Insulin plays a role in the regulation of hybrid receptor formation [28].

Mitogenic actions transmitted by the type II IGF receptor are only sporadically reported [29, 30]. This receptor plays a role in lysosomal targeting of the IGFs, especially of IGF-II, and their subsequent degradation, as well as in cell motility, and it promotes exocytosis in insulin-secreting cells [23, 31, 32]. Furthermore, this receptor functions as a tumour suppressor gene [33, 34], and it is required for proliferin-induced angiogenesis [35]. Besides IGF-II, the type II IGF receptor also binds mannose-6-phosphate and retinoic acid [36]. The imprinted type II IGF receptor is crucial for regulating normal growth and viability, as demonstrated in mice with a targeted disruption of this receptor [37, 38]. Loss of imprinting occurs in acute myeloid leukaemia [39]. Recently, a role for the type II IGF receptor in cell adhesion and growth regulation of myeloma cells, a human B cell neoplasia, has been suggested [40].

The type II IGF receptor contains a long extracellular domain and a relatively short intracellular domain. G

proteins appear to be important for signal transduction. While EGF and PDGF enhance transcription of the type I IGF receptor gene, the type II IGF receptor plays a role in activation of latent TGF-β [41, 42].

IGF-binding proteins

To date six IGF-binding proteins (IGFBP-1 through -6) have been cloned and characterized [43, 44]. They bind IGF-I and/or IGF-II with varying affinities, but are unable to bind insulin. These peptides contain 16 cystine residues which are conserved during evolution. Their molecular weights (including sugar chains) vary between 24 and 45 kDa. In the circulation IGFBP-3 is the dominant IGFBP. IGFBP-3 not only interacts with IGFs; it also interacts with an acid-labile subunit (ALS), which leads to the formation of a 150-kDa IGFBP complex with an estimated half-life in the circulation of approximately 18 h [45]. In contrast with most other IGFBPs, IGFBP-3 and ALS are both GH-dependent. The IGFBPs are produced by many cells. IGFBP-1 and -2 can interact with the cell membrane and the extracellular matrix by an RGD integrin-binding sequence [44]. Furthermore, a specific receptor for IGFBP-3 has been reported [46], which shows identity with the TGF-β receptor [47]. In addition, IGFBPs possess glycosylation or phosphorylation sites [44] which modulate the binding of the IGFs to their specific IGFBPs.

In general, IGFBPs prolong the half-life and diminish the hypoglycaemic effect of the IGFs, and they modulate the actions of the IGFs by sequestering them away from their receptors. In addition, direct effects of IGFBP-3 on the type I IGF receptor have been demonstrated which could either facilitate [48] or inhibit [49] IGF-I binding. IGFBP-3 also exerts IGF-independent effects on growth, e.g. by stimulating apoptosis [50]. In this respect IGFBP-3 functions as a tumour suppressor [51]. The IGFBP-3 gene itself can be regulated by the tumour suppressor p53 [50, 52] and by TGF-β [53].

Recently, homologous proteins (IGFBP-7 to -10) which bind IGFs with low affinity but bind insulin with high affinity have been discovered [54–56]. Since these proteins can also bind insulin, they were called IGFBP-related proteins (4th International Symposium on IGFs, Tokyo, October 1997).

IGF proteases and IGFBP proteases

Specific proteases for IGFs have been described which favour degradation and subsequent clearance of the IGFs. An acid protease present in serum generates des-(1-3)-IGF-I, a variant which has been identified in the brain as well [57–59]. Although the physiological meaning of this variant is still uncertain, it is believed to have a higher biological activity since it lacks affinity for IGFBPs [60]. It cannot be excluded, however, that the split-off tripeptide itself is of physiological importance [61]. Regulation of the IGF-I protease occurs by the serine protease inhibitor Spi 2.1. Reduced levels of Spi 2.1 in GH-deficient rats may be responsible for enhanced IGF-I protease activity in these animals, showing an additional mechanism by which GH regulates IGF-I bioavailability [62].

IGFBP action can be regulated both systemically and locally by IGFBP proteases. Specific proteases for IGFBP-1 through -6 have been identified, including kallikreins, cathepsins and matrix metalloproteinases [63–65].

In pregnancy and several disease states such as severe critical illness, chronic renal failure and GHD, activities of IGFBP-3 proteases are increased [66–68]. It has been shown that proteolytically cleaved IGFBP fragments have a diminished affinity for IGFs, and therefore proteolysis is postulated to enhance IGF action [64, 66, 69].

The above-described constituents delineate the GH-IGF axis and form part of a complex network which regulates growth and development of cells and tissues, including the immunological system (fig. 1).

The GH-IGF axis in lymphoid organs

The function of pituitary hormones and IGF-I on B cell development in bone marrow are extensively discussed by Foster et al. in this issue. In the next section we will address the role of GH and IGFs in the physiology of the thymus and spleen.

The thymus

The thymus is a primary lymphoid organ in which bone marrow-derived T cell precursors undergo a complex process of maturation. During this process, immature T cells undergo rearrangement of genes encoding T cell receptors for antigen. Positive and negative selection leads to mature T cells that recognize antigens in the context of either major histocompatibility (MHC) class I or class II, whereas autoreactive T cells are eliminated via apoptosis. This T cell maturation process is orchestrated by cytokines and growth factors derived from either lymphocytes or thymic epithelial cells (TECs) and by direct cellular interactions with neighbouring cells like TECs [70, 71]. That the thymus can be subject to endocrine control via the GH-IGF axis is indicated by the presence of receptors for GH on thymic lymphocytes [72] and on a thymic epithelial cell line [73], as well as the presence of type I IGF receptors on thymic lymphocytes [74, 75].

Additionally, rat thymocytes and mouse thymic lymphoma cells express type II IGF receptors [74]. GH messenger RNA (mRNA) and protein expression in the human thymus is located along the thymus capsule, the subcapsular cortex and within the septa [76]. In the thymus of normal mice, rats and humans IGF-II protein and mRNA are detectable, but IGF-I expression is rather low [77, 78]. The presence of IGFBP-2 to -6 and IGFBP-4 protease in the murine thymus [79, 80] suggests that these proteins modulate the actions of IGFs in the thymus.

Immunodeficiencies have been reported in GHD, in hypophysectomized rats with impairment of the humoral, cell-mediated, and autoimmune responses [81–83] and in Snell and Ames dwarf mice [84, 85]. In these animals a thymic deficiency exists with early involution and decreased production of lymphocytes. In the Snell-Bagg strain the cortex was found to be much thinner than in wild-type mice, and there was a predominance of the medulla [86–88].

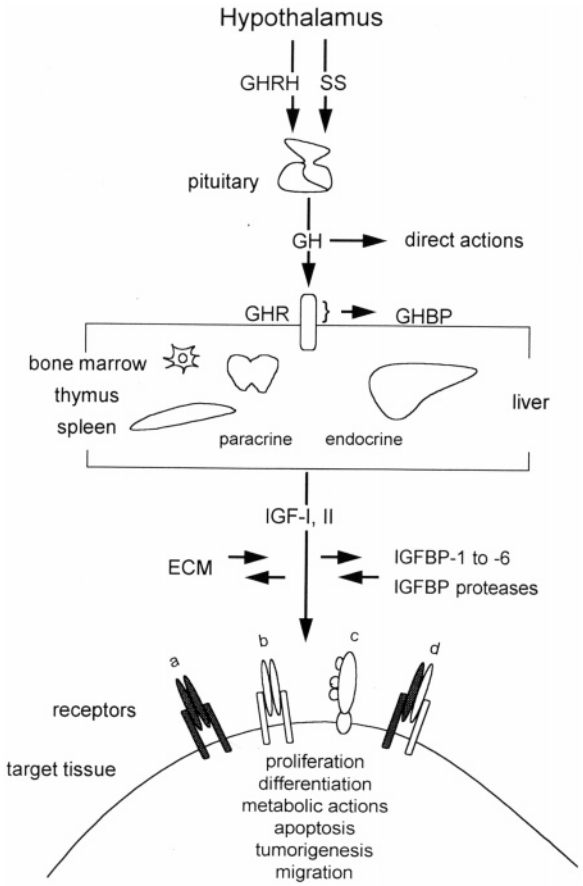

Figure 1. Schematic diagram of actions and interactions of the constituents comprising the GH-IGF axis. GHRH, growth hormone-releasing hormone; SS, somatostatin; GH, growth hormone; GHR, GH receptor; GHBP, GH-binding protein; IGF-I, -II, insulin-like growth factor I, II; IGFBP, IGF-binding protein; ECM, extracellular matrix; receptors: a: insulin receptor; b: type I IGF receptor; c: type II IGF receptor; d: insulin/IGF-I hybrid receptor.

Treatment with GH has divergent effects. First, it can increase thymic growth and cellular content and improve thymic architecture in growing and aged rats and mice and in GHD rats and mice [82, 89–93]. Second, it can reverse or prevent thymic involution [94] and third, GH can stimulate repopulation of the thymus after irradiation or cyclosporin-induced damage [95, 96]. In addition, mice injected with antiserum to GH develop thymic atrophy and wasting syndrome [97, 98]. Likewise, in transgenic mice overexpressing GH, the weight of the thymus was increased [99, 100].

It has been suggested that the effects of GH on thymic growth are indirect, in the sense that GH treatment enhances the release of IGF-I from TECs, which stimulates thymocyte proliferation [73, 101]. Remarkably, thymic size as well as the developmental pattern of thymus growth mimic endogenous plasma IGF-I concentrations [102]. A good correlation between plasma IGF-I and thymulin, a peptide produced by TECs, has been observed in acromegalic patients. This suggests a role for GH and IGF-I in the control of thymic hormonal function in humans [103].

Many of the effects described for GH were also obtained with IGF-I, as demonstrated in normal and GH-deficient mice and rats [82, 90, 96, 104–106]. In addition, IGF-I stimulates the repopulation of the atrophied thymus in diabetic rats [107]. In general, IGF-I is more effective than GH in restoration of the thymus, but combination therapy gives the best result [96]. These data suggest that patients suffering from immune deficiencies can benefit from treatment with GH and/or IGF-I.

The effects of IGF-II are not clear at present. The observed IGF-II expression in the human and rat thymus suggests an important role for this peptide [77]. However, although exogenous IGF-II stimulates growth of the thymus in Snell dwarf mice, it does so to a lesser extent than IGF-I [108–110]. In transgenic mice overexpressing human IGF-II under the transcriptional control of the H2Kb promoter, thymus weight was increased and involution delayed. Similar results were obtained in IGF-II transgenic Snell dwarf mice, showing that in these GH and IGF-I deficient animals IGF-II alone was capable of stimulating the growth of this organ [110]. In both transgenic models growth of the thymus was accompanied by an increased number of thymocytes, and maturation followed the normal sequence of events [111, 112]. The endogenous H2Kb gene is mainly expressed in the mature T cells which reside in the medulla. A similar pattern of expression exists in our transgenic mice with respect to the mRNA

expression pattern of IGF-II, which is mainly located in thymocytes in the medulla as shown by in situ hybridization [78, 113]. Expression of IGF-II protein is less abundant than mRNA expression and can be seen in T lymphocytes of the medulla and possibly in thymic epithelial cells [78, 113]. This high expression of IGF-II in the thymus may be responsible for the observed growth stimulation. Other IGF-II transgenic mouse models, which all have elevated serum IGF-II concentrations, did not show increased growth of the thymus [114–116]. This suggests that autocrine/paracrine rather than endocrine mechanisms are responsible for the increase in size.

Further studies are needed in order to unravel the interplay between the above-mentioned constituents and their roles in the regulation of cell proliferation, differentiation and apoptosis in lymphoid tissues.

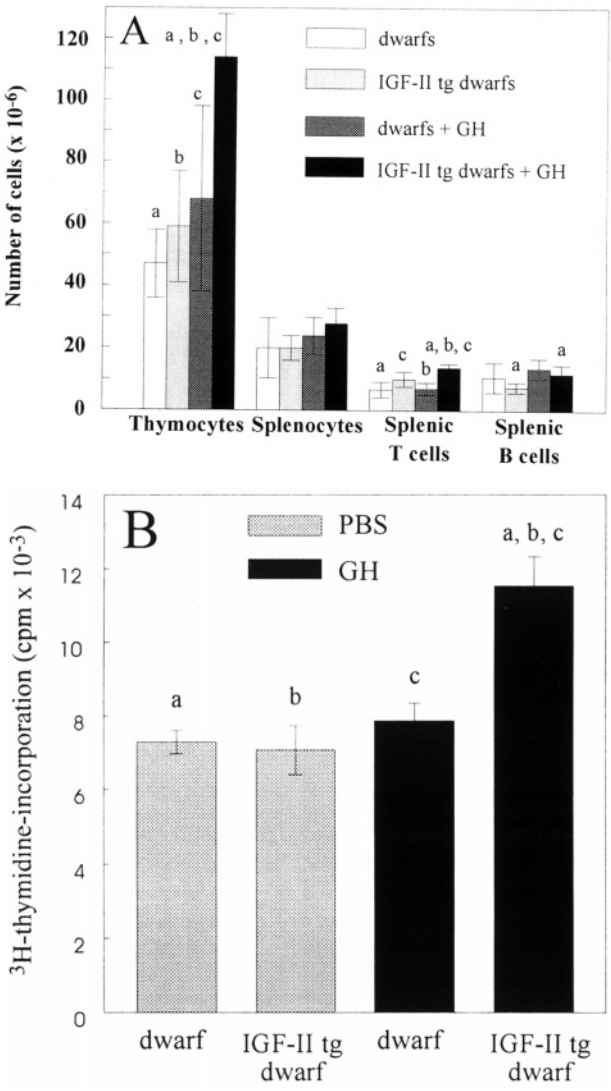

Figure 2. IGF-II transgenic and control dwarf mice were treated with 16.6 mU recombinant human GH per day for 4 weeks after which thymic and splenic weight and cellularity were assessed (*A*). T cells and B cells were identified by flow cytometry using anti-CD3 and anti-immunoglobulin M (IgM), respectively (*B*). Thymocyte proliferation was measured by culturing freshly isolated thymocytes for 18 h in the presence of ^{3}H-thymidine. The data represent mean values $\pm$ SD ($n = 4$). For a given cell type, values indicated by the same letter (a, b or c) are significantly different ($P < 0.05$).

Spleen

Mature B and T cells reside in the white pulp of the spleen where they respond to blood-borne antigens. For functional studies in animals, mature B and T cells are usually obtained from the spleen, whereas mature cells from humans are usually isolated from peripheral blood. Mature B and T cells express GH receptors and type I IGF receptors. Type I IGF receptors and insulin/IGF-I hybrid receptors were also found on peripheral monocytes and natural killer (NK) cells. They are not present, however, in similar quantities on the different cell types [73–75, 117–122].

GH is produced by rodent splenocytes [123] and human peripheral blood mononuclear cells [124]. The presence of IGF-I in activated T and B cells, leukocytes, macrophages and in minor quantities in the spleen implies an important role of these factors in the regulation of immune function by paracrine and/or autocrine mechanisms [77, 125–131]. Indeed, an autocrine role for GH in human cultured lymphocytes has been demonstrated [132]. Several experimental animal models indicate that endocrine effects of GH and IGFs on the spleen exist.

The role of GH becomes apparent in GH-deficient rodents, where spleen weights as well as the number of T lymphocytes, B cells and the NK activity of spleen lymphocytes are significantly lower than in normal animals [133–135]. Increased growth of this organ has been obtained by treating normal rats, hypophysectomized rats and Snell dwarf mice with GH as well as in transgenic mice overexpressing GH [82, 136–139].

Besides GH, IGF-I is important for splenic growth, as shown in normal mice selected for high plasma IGF-I levels. In these animals spleen weight was higher compared with mice with a low IGF-I level [102]. Growth of the spleen was stimulated by administration of IGF-I and/or IGF-II in normal rats and mice [104–106, 136, 137, 140], in GHD mice and rats [82, 90], and in IGF-I transgenic mice [141, 142]. A similar increase in spleen weight was observed in patients with GH insensitivity syndrome during IGF-I treatment [143].

In normal animals, GH and IGF-I increased the number of B lineage cells in the spleen and bone marrow but

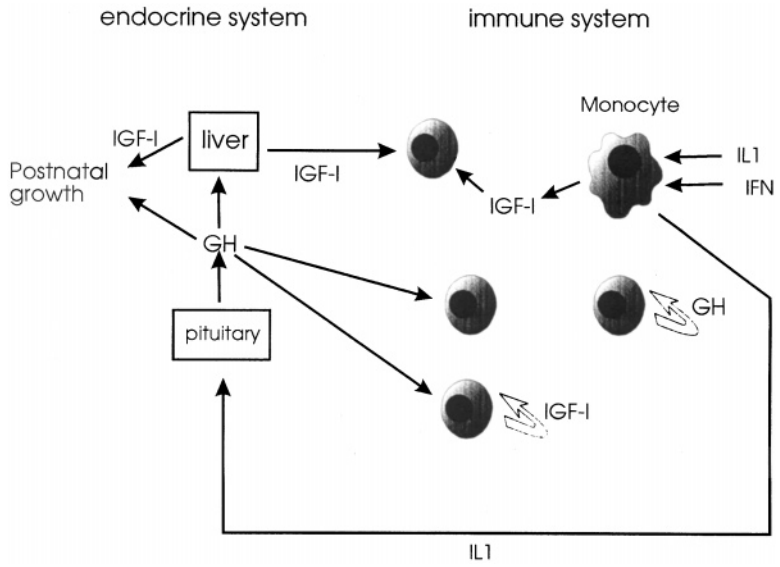

Figure 3. Possible role of GH and IGF-I as cytokines or endocrine modulators of the immune system. IL1 is given as an example of how cytokines can act on the pituitary [3].

did not restore the frequency of bone marrow pre-B cells to normal [106, 144, 145]. T4 treatment, however, gave rise to reconstitution of the number and frequency of B lineage cells [146, 147; see also Forster et al. in this issue].

Although IGF-I increases the size of the T and B cell compartments in both normal and dwarf mice, IGF-II overexpression in transgenic mice only stimulated the number of thymocytes and T cells in the spleen [112]. The number of mature B cells in spleen and bone marrow was not affected. Furthermore, overexpression of IGF-II in transgenic dwarf mice, which do not show circulating levels of IGF-I, did not affect B cell development either [111]. These results imply that IGF-II cannot stimulate B cell development in mice, even in the absence of IGF-I.

Since GH regulates the expression of the IGFs, possible synergistic effects between GH and IGFs should be taken into account. We observed synergistic effects between GH and IGF-II in 10-week-old IGF-II transgenic dwarf mice which were treated with GH for 4 weeks. They showed an increase in the number of thymocytes in the thymus and mature T cells in the spleen, whereas the number of B cells was unaffected (fig. 2A). This result is in accordance with the synergistic effect of IGF-II and GH on thymocyte proliferation (fig. 2B) and suggests that GH and IGF-II can act in a synergistic fashion on T cell development, but not on B cell development. Splenic growth is variably influenced by IGFBPs. In IGFBP-3 transgenics a significant increase has been observed, whereas in IGFBP-1 transgenics spleen weight was only marginally changed as compared with normal age-matched controls [148, 149]. In IGFBP-2 knockout mice the spleen size is decreased [150]. A possible requirement of IGFBP-2 for splenic growth is confirmed by the observation that during foetal life IGFBP-2 in mice is expressed in the anterior splanchnic mesodermal plate [150].

In addition, IGFBPs are produced by many cells of the immune system. In human foetal tissues, mRNAs of IGFBP-2 to -6 are detectable at low to moderate levels in the spleen. In contrast, IGFBP-1 [79] and ALS are undetectable [151]. IGFBPs are also produced by normal human lymphocytes. Unstimulated lymphocytes express only IGFBP-2 and -3, whereas after stimulation IGFBP-4 and -5 are detectable as well. IGFBP-1 remains undetectable, however [130]. This opens up the possibility that the actions of endocrine or locally produced IGFs can be modulated via production of IGFBPs by cells from the immune system.

The role of IGFBPs in modulating actions of IGF-II is being investigated by us in IGF-II transgenic mice. It is remarkable that transgenic mice overexpressing IGF-II do not show an increase in size of the spleen, which is in sharp contrast with data obtained for the thymus in these animals [110]. Endogenous expression of IGF-II mRNA and protein in the spleen was low. As in the thymus, there was a high expression of the IGF-II

mRNA transgene in the spleen of the transgenic animals localized in the white pulp. IGF-II protein levels were, however, rather low, which may be the result of rapid transport through the circulation [78, 113]. In contrast to the situation in the thymus, where IGFBP-3 mRNA expression was undetectable by in situ hybridization, a marked increase of IGFBP-3 mRNA in the marginal zone of the spleen of IGF-II transgenic mice was observed. This zone surrounds the white pulp of the spleen [78, 113]. Therefore, an explanation for the apparently conflicting results between spleen and thymus could be an inhibiting action of IGFBP-3 on the IGF-II-induced growth in the spleen by either an IGF-dependent or IGF-independent mechanism.

In this respect it would be interesting to investigate the occurrence of apoptosis in these organs, since several authors have shown that IGFs can inhibit apoptosis [32], whereas on the contrary IGFBP-3 stimulates this process of programmed cell death [52]. In addition, tissue-specific expression of IGFBPs with a relatively high affinity for IGF-II could also be responsible for tissue-specific effects of IGF-II [43–45].

Immune responses

In GHD rats and mice, the immune response is impaired. GH and IGF-I can improve the graft-vs.-host reactions, development of contact dermatitis in response to dinitrochlorobenzene and antibody production following primary and secondary antigen challenge [86, 89, 91, 106, 152–154]. The enhancement of the immune response obtained in ageing mice and monkeys by treatment with GH and IGF-I suggests new avenues for the treatement of declining immune function as observed during ageing [106, 145]. In GHD patients, however, immune function seems to be only marginally affected [155, 156]. Therefore the use of GH and IGF-I as immunotherapies requires further analysis.

Summary and perspectives

It has been established that GH and the IGFs affect development and function of the immune system. Although they do not seem to be essential for lymphopoiesis, they can modulate immune responses. At present, benefits can be expected from treating humans with GH and/or IGFs in order to prevent a decline in immune function during ageing [118].

From gene manipulation experiments in mice, a local growth-promoting effect on the thymus has been shown in IGF-II-overexpressing animals, leading to an increased number of T lymphocytes and a normal maturation of the T lymphocyte subsets. In the spleen increased growth does not become apparent, despite high expression of the transgene. This is probably due to modulating effects of specifically induced IGFBP-3.

The specific roles and importance of the IGFBPs and IGFBP proteases in the immune system await further elucidation.

In contrast to the knockout models of the IGFs and their specific receptors, the IGFBP-2, -4 and -6 knockouts demonstrated nearly normal growth, whereas in IGFBP-2 knockout mice growth of the spleen was diminished. In none of these animals, however, has functioning of the immune system been extensively investigated.

The expression of GH and IGFs in the immune system opens up the possibility that GH and IGFs are not only involved in endocrine control of the immune system but also play a role as local growth and differentiation factors (cytokines). As depicted in figure 3, endocrine control of GH could be direct or mediated via endocrine or autocrine/paracrine IGF-I. In addition, GH could act as an autocrine or paracrine factor. Although several effects of GH on the function of leukocytes are mediated by IGF-I, most in vitro effects of GH have been shown to be direct. In addition, IGF-I expression in the immune system has been shown to be regulated by cytokines, like interleukin-1 (IL-1) and interferon-γ [157, 158], alluding to a cytokine-like function of IGF-I. Moreover, the finding that expression of GH in murine bone marrow cells does not depend on the transcription factor Pit-1 [159] suggests an alternative regulation model for this hormone in the immune system. It has also been established that the immune system feeds back to the endocrine system at the level of the hypothalamus and pituitary (fig. 3).

Recently it has been reported that in IL-6 transgenic mice growth retardation was correlated with low IGF-I levels [160]. These kinds of studies can be helpful in unravelling the cross-talk between IGFs and other components, for example interleukins in immune function.

Acknowledgements. The authors thanks Mr. R. J. Bloemen and Mrs H. E. M. Helsloot for their help in the preparation of the manuscript. We are grateful to Drs E. L. Hooghe-Peters, R. Hooghe, M. Jansen and J. A. Koedam for critical reading of the manuscript.

1 Clark R. (1997) The somatogenic hormones and insulin-like growth factor-1: stimulators of lymphopoiesis and immune function. Endocr. Rev. **18:** 157–179
2 Kooijman R., Hooghe-Peters E. L. and Hooghe R. (1996) Prolactin, growth hormone and insulin-like growth factor-1 in the immune system. Adv. Immunol. **63:** 377–454
3 Mandrup-Poulsen T., Nerup J., Reimers J. I., Pociot F., Andersen H. U., Karlsen A., Bjerre U. and Bergholdt R. (1995) Cytokines and the endocrine system.1. The immunoendocrine network. Eur. J. Endocrinol. **133:** 660–671
4 Auernhammer C. J. and Strasburger C. J. (1995) Effects of growth hormone and insulin-like growth factor on the immune system. Eur. J. Endocrinol. **133:** 635–645

5 Palmetshofer A., Zechner D., Luger T. A. and Barta A. (1995) Splicing variants of the human growth hormone mRNA: detection in pituitary, mononuclear cells and dermal fibroblasts. Mol. Cell Endocrinol. **113:** 225–234
6 Schanke J. T., Conwell C. M., Durning M., Fisher J. M. and Golos T. G. (1997) Pit-1 growth hormone factor 1 splice variant expression in the rhesus monkey pituitary gland and the rhesus and human placenta. J. Clin. Endocrinol. Metab. **82:** 800–807
7 Pfaeffle R., Kim C., Otten B., Wit J. M., Eiholzer U., Heimann G. and Parks J. (1996) Pit-1: clinical aspects. Horm. Res. **45:** 25–28
8 Cohen L. E., Wondisford F. E. and Radovick S. (1996) Role of Pit-1 in the gene expression of growth hormone, prolactin and thyrotropin. Endocrinol. Metabol. Clin. North Am. **25:** 523–540
9 Argetsinger L. S. and Carter-Su C. (1996) Mechanism of signaling by growth hormone receptor. Physiol. Rev. **76:** 1089–1107
10 Goffin V. and Kelly P. A. (1996) Prolactin and growth hormone receptors. Clin. Endocrinol. (Oxf.) **45:** 247–255
11 Han Y., Leaman D. W., Watling D., Rogers N. C., Groner B., Kerr I. M. et al. (1996) Participation of JAK and STAT proteins in growth hormone-induced signaling. J. Biol. Chem. **271:** 5947–5952
12 Harding P. A., Wang X., Okada S., Chen W. Y., Wan W. and Kopchick J. J. (1996) Growth hormone (GH) and a GH antagonist promote GH receptor dimerization and internalization. J. Biol. Chem. **271:** 6708–6712
13 Sobrier M. L., Dastot F., Duquesnoy P., Kandemir N., Yordam N., Goossens M. et al. (1997) Nine novel growth hormone receptor gene mutations in patients with Laron syndrome. J. Clin. Endocrinol. Metab. **82:** 435–437
14 Baumann G. (1996) Growth hormone-binding proteins – an overview. Acta Paediatr. **85:** 95–97
15 Postel-Vinay M. C. (1996) Growth hormone-binding protein: biological significance. Acta Paediatr. **85:** 98–101
16 Salmon W. D. Jr. and Burkhalter V. J. (1997) Stimulation of sulfate and thymidine incorporation into hypophysectomized rat cartilage by growth hormone and insulin-like growth factor-I in vitro: the somatomedin hypothesis revisited. J. Lab. Clin. Med. **129:** 430–438
17 Stewart C. E. H. and Rotwein P. (1996) Growth, differentiation and survival: multiple physiological functions for insulin-like growth factors. Physiol. Rev. **76:** 1005–1026
18 Le Roith D., King G. and Flier J. S. (1997) Insulin-like growth factors. N. Engl. J. Med. **336:** 633–639
19 Louvi A., Accili D. and Efstratiadis A. (1997) Growth-promoting interaction of IGF-II with the insulin receptor during mouse embryonic development. Dev. Biol. **189:** 33–48
20 Cheatham B. and Kahn C. R. (1995) Insulin action and the insulin signaling network. Endocr. Rev. **16:** 117–142
21 Morrione A., Valentinis B., Resnicoff M., Xu S. Q. and Baserga R. (1997) The role of mGrb10Alpha in insulin-like growth factor I-mediated growth. J. Biol. Chem. **272:** 26382–26387
22 Baserga R., Hongo A., Rubini M., Prisco M. and Valentinis B. (1997) The IGF-I receptor in cell growth, transformation and apoptosis. Biochim. Biophys. Acta Rev. Cancer **1332:** F105–F126
23 Leventhal P. S. and Feldman E. L. (1997) Insulin-like growth factors as regulators of cell motility – signaling mechanisms. Trends Endocrinol. Metab. **8:** 1–6
24 Werner H. and LeRoith D. (1996) The role of the insulin-like growth factor system in human cancer. Adv. Cancer Res. **68:** 183–223
25 Singleton J. R., Dixit V. M. and Feldman E. L. (1996) Type I insulin-like growth factor receptor activation regulates apoptotic proteins. J. Biol. Chem. **271:** 31791–31794
26 Valerio G., Bond H. M., Badolato R., Petrella A., Di Maio S., Salerno M. et al. (1997) Expression of growth hormone receptor by peripheral blood lymphocytes in children: evaluation in clinical conditions of impaired growth. Clin. Endocrinol. (Oxf.) **47:** 329–335
27 Hattori Y., Vera J. C., Rivas C. I., Bersch N., Bailey R. C., Geffner M. E. et al. (1996) Decreased insulin-like growth factor I receptor expression and function in immortalized African Pygmy T cells. J. Clin. Endocrinol. Metab. **81:** 2257–2263
28 Federici M., Lauro D., D'Adamo M., Giovannone B., Porzio O., Mellozzi M. et al. (1998) Expression of insulin/IGF-I hybrid receptors is increased in skeletal muscle of patients with chronic primary hyperinsulinemia. Diabetes **47:** 87–92
29 Tally M. and Hall K. (1990) Insulin-like growth factor II effects mediated through insulin-like growth factor II receptors. Acta Paediatr. Scand. **79** Suppl. 367**:** 67–73
30 Zhang Q. M., Hall K. and Tally M. (1996) Partial purification of an IGF-II receptor binding protein from the erythroleukemia cell line K562. Mol. Cell Biol. **154:** 47–54
31 Minniti C. P., Kohn E. C., Grubb J. H., Sly W. S., Oh Y., Muller H. L. et al. (1992) The insulin-like growth factor II (IGF-II)/mannose 6-phosphate receptor mediates IGF-II-induced motility in human rhabdomyosarcoma cells. J. Biol. Chem. **267:** 9000–9004
32 Zhang Q. M., Tally M., Larsson O., Kennedy R. T., Huang L., Hall K. and Berggren P. O. (1997) Insulin-like growth factor II signaling through the insulin-like growth factor II mannose-6-phosphate receptor promotes exocytosis in insulin-secreting cells. Proc. Natl. Acad. Sci. USA **94:** 6232–6237
33 Yamada T., De Souza A. T., Finkelstein S. and Jirtle R. L. (1997) Loss of the gene encoding mannose 6-phosphate insulin-like growth factor II receptor is an early event in liver carcinogenesis. Proc. Natl. Acad. Sci. USA **94:** 10351–10355
34 Hankins G. R., De Souza A. T., Bentley R. C., Patel M. R., Marks J. R., Iglehart J. D. et al. (1996) M6P/IGF2 receptor: a candidate breast tumor suppressor gene. Oncogene **12:** 2003–2009
35 Volpert O., Jackson D., Bouck N. and Linzer D. I. H. (1996) The insulin-like growth factor II/mannose 6-phosphate receptor is required for proliferin-induced angiogenesis. Endocrinology **137:** 3871–3876
36 Kang J. X., Li Y. Y. and Leaf A. (1997) Mannose-6-phosphate/insulin-like growth factor-II receptor is a receptor for retinoic acid. Proc. Natl. Acad. Sci. USA **94:** 13671–13676
37 Lau M. M. H., Stewart C. E. H., Liu Z., Bhatt H., Rotwein P. and Stewart C. L. (1994) Loss of the imprinted IGF2/cation-independent mannose 6-phosphate receptor results in fetal overgrowth and perinatal lethality. Genes Dev. **8:** 2953–2963
38 Ludwig T., Eggenschwiler J., Fisher P., D'Ercole A. J., Davenport M. L. and Efstratiadis A. (1996) Mouse mutants lacking the type 2 IGF receptor (IGF2R) are rescued from perinatal lethality in Igf2 and Igf1r null backgrounds. Dev. Biol. **177:** 517–535
39 Wu H. K., Weksberg R., Minden M. D. and Squire J. A. (1997) Loss of imprinting of human insulin-like growth factor II gene, IGF2, in acute myeloid leukemia. Biochem. Biophys. Res. Commun. **231:** 466–472
40 Nishiura T., Karasuno T., Yoshida H., Nakao H., Ogawa M., Horikawa Y. et al. (1996) Functional role of cation-independent mannose 6-phosphate/insulin-lik growth factor II receptor in cell adhesion and proliferation of a human myeloma cell line OPM-2. Blood **88:** 3546–3554
41 Dennis P. A. and Rifkin D. B. (1991) Cellular activation of latent transforming growth factor Beta requires binding to the cation-independent mannose 6-phosphate/insulin-like growth factor type II receptor. Proc. Natl. Acad. Sci. USA **88:** 580–584
42 De Bleser P. J., Jannes P., Van Buul-Offers S. C., Hoogerbrugge C. M., Van Schravendijk C. F. H., Niki T. et al. (1995) Insulinlike growth factor-II/mannose 6-phosphate receptor is expressed on CCl 4-exposed rat fat-storing cells and facilitates activation of latent transforming growth factor-beta in cocultures with sinusoidal endothelial cells. Hepatology **21:** 1429–1437

43 Rajaram S., Baylink D. J. and Mohan S. (1997) Insulin-like growth factor-binding proteins in serum and other biological fluids: regulation and functions. Endocr. Rev. **18:** 801–831

44 Clemmons D. R. (1997) Insulin-like growth factor binding proteins and their role in controlling IGF actions. Cytokine Growth Factors Rev. **8:** 45–62

45 Zapf J. (1995) Physiological role of the insulin-like growth factor binding proteins. Eur. J. Endocrinol. **132:** 645–654

46 Oh Y., Muller H. L., Pham H. and Rosenfeld R. G. (1993) Demonstration of receptors for insulin-like growth factor binding protein-3 on Hs578T human breast cancer cells. J. Biol. Chem. **268:** 26045–26048

47 Leal S. M., Liu Q. J., Huang S. S. and Huang J. S. (1997) The type V transforming growth factor Beta receptor is the putative insulin-like growth factor-binding protein 3 receptor. J. Biol. Chem. **272:** 20572–20576

48 Conover C. A. (1992) Potentiation of insulin-like growth factor (IGF) action by IGF-binding protein-3: studies of underlying mechanism. Endocrinology **130:** 3191–3199

49 Mohseni-Zadeh S. and Binoux M. (1997) Insulin-like growth factor (IGF) binding protein-3 interacts with the type IGF receptor, reducing the affinity of the receptor for its ligand: an alternative mechanism in the regulation of IGF action. Endocrinology **138:** 5645–5648

50 Buckbinder L., Talbott R., Velasco-Miguel S., Takenaka I., Faha B., Seizinger B. R. et al. (1995) Induction of the growth inhibitor IGF-binding protein 3 by p53. Nature **377:** 646–649

51 Valentinis B., Bhala A., DeAngelis T., Baserga R. and Cohen P. (1995) The human insulin-like growth factor (IGF) binding protein-3 inhibits the growth of fibroblasts with a targeted disruption of the IGF-I receptor gene. Mol. Endocrinol. **9:** 361–367

52 Rajah R., Valentinis B. and Cohen P. (1997) Insulin like growth factor (IGF)-binding protein-3 induces apoptosis and mediates the effects of transforming growth factor-β-1 on programmed cell death through a p53- and IGF-independent mechanism. J. Biol. Chem. **272:** 12181–12188

53 Youngman O., Muller H. L., Ng L. and Rosenfeld R. G. (1995) Transforming growth factor-β-induced cell growth inhibition in human breast cancer cells is mediated through insulin-like growth factor-binding protein-3 action. J. Biol. Chem. **270:** 13589–13592

54 Wilson E. M., Oh Y. and Rosenfeld R. G. (1997) Generation and characterization of an IGFBP-7 antibody: identification of 31kD IGFBP-7 in human biological fluids and Hs578T human breast cancer conditioned media. J. Clin. Endocrinol. Metab. **82:** 1301–1303

55 Kim H. S., Nagalla S. R., Oh Y., Wilson E., Roberts C. T. Jr. and Rosenfeld R. G. (1997) Identification of a family of low-affinity insulin-like growth factor binding proteins (IGFBPs): characterization of connective tissue growth factor as a member of the IGFBP superfamily. Proc. Natl. Acad. Sci. USA **94:** 12981–12986

56 Yamanaka Y., Wilson E. M., Rosenfeld R. G. and Oh Y. (1997) Inhibition of insulin receptor activation by insulin-like growth factor binding proteins. J. Biol. Chem. **272:** 30729–30734

57 Sara V. R., Carlsson-Skwirut C., Andersson C., Hall E., Sjogren B., Holmgren A. et al. (1986) Characterization of somatomedins from human fetal brain: identification of a variant form of insulin-like growth factor I. Proc. Natl. Acad. Sci. USA **83:** 4904–4907

58 Yamamoto H. and Murphy L. J. (1994) Generation of Des-(1–3) insulin-like growth factor-I in serum by an acid protease. Endocrinology **135:** 2432–2439

59 Van den Brande J. L. (1992) Structure of the human insulin-like growth factors: relationship to function. In: The Insulin-like Growth Factors. Structure and Biological Functions, pp. 12–44, Schofield P. N. (ed.), Oxford University Press, Oxford

60 Jansson M., Uhlen M. and Nilsson B. (1997) Structural changes in insulin-like growth factor (IGF) I mutant proteins affecting binding kinetic rates to IGF binding protein 1 and IGF-I receptor. Biochemistry **36:** 4108–4117

61 Guan J., Williams C. E., Skinner S. J. M., Mallard E. C. and Gluckman P. D. (1996) The effects of insulin-like growth factor (IGF)-1, IGF-2 and des-IGF-1 on neuronal loss after hypoxic-ischemic brain injury in adult rats: evidence for a role for IGF binding proteins. Endocrinology **137:** 893–898

62 Maake C., Yamamoto H. and Murphy L. J. (1997) The growth hormone dependent serine protease inhibitor, Spi 2.1 inhibits the des (1–3) insulin-like growth factor-I generating protease. Endocrinology **138:** 5630–5636

63 Manes S., Mira E., Barbacid M. D., Cipres A., Fernandez-Resa P., Buesa J. M. et al. (1997) Identification of insulin-like growth factor-binding protein-1 as a potential physiological substrate for human stromelysin-3. J. Biol. Chem. **272:** 25706–25712

64 Fowlkes J. L. (1997) Insulin-like growth factor-binding protein proteolysis – an emerging paradigm in insulinlike growth factor physiology. Trends Endocrinol. Metab. **8:** 299–306

65 Rajah R., Bhala A., Nunn S. E., Peehl D. M. and Cohen P. (1996) 7S nerve growth factor is an insulin-like growth factor-binding protein protease. Endocrinology **137:** 2676–2682

66 Blat C., Villaudy J. and Binoux M. (1994) In vivo proteolysis of serum insulin-like growth factor (IGF) binding protein-3 results in increased availability of IGF to target cells. J. Clin. Invest. **93:** 2286–2290

67 Timmins A. C., Cotterill A. M., Hughes S. C. C., Holly J. M. P., Ross R. J. M., Blum W. et al. (1996) Critical illness is associated with low circulating concentrations of insulin-like growth factors-I and -II, alterations in insulin-like growth factor binding proteins and induction of an insulin-like growth factor binding protein 3 protease. Crit. Care Med. **24:** 1460–1466

68 Koedam J. A., Hoogerbrugge C. M. and Van Buul-Offers S. C. (1998) IGFBP-3 protease activity in Snell normal and Pit-1 deficient dwarf mice. J. Endocrinol. **156:** 295–303

69 Collett-Solberg P. F. and Cohen P. (1996) The role of the insulin-like growth factor binding proteins and the IGFBP proteases in modulating IGF action. Endocrinol. Metabol. Clin. North Am. **25:** 591–614

70 Dardenne M. and Savino W. (1994) Control of thymus physiology by peptidic hormones and neuropeptides. Immunol. Today **15:** 518–523

71 Janeway C. A. Jr. and Travers P. (1996) Immunobiology. The Immune System in Health and Disease. Curr. Biol. (Lond.)

72 Arrenbrecht S. (1974) Specific binding of growth hormone to thymocytes. Nature **252:** 255–257

73 Lin B., Kinoshita Y., Hato F. and Tsuji Y. (1997) Enhancement of DNA synthetic activity of thymic lymphocytes by the culture supernatant of thymus epithelial cells stimulated by growth hormone. Cell. Mol. Biol. **43:** 351–359

74 Verland S. and Gammeltoft S. (1989) Functional receptors for insulin-like growth factors I and II in rat thymocytes and mouse thymoma cells. Mol. Cell. Endocrinol. **67:** 207–216

75 Kooijman R., Scholtens L. E., Rijkers G. T. and Zegers B. J. M. (1995) Type I insulin-like growth factor receptor expression in different developmental stages of human thymocytes. J. Endocrinol. **147:** 203–209

76 Maggiano N., Piantelli M., Ricci R., Larocca L. M., Capelli A. and Ranelletti F. O. (1994) Detection of growth hormone-producing cells in human thymus by immunohistochemistry and non-radioactive in situ hybridization. J. Histochem. Cytochem. **42:** 1349–1354

77 Geenen V., Achour I., Robert F., Vandersmissen E., Sodoyez J. C., Defresne M. P. et al. (1993) Evidence that insulin-like growth factor 2 (IGF2) is the dominant thymic peptide of the insulin superfamily. Thymus **21:** 115–127

78 Van Der Ven L. T. M., Roholl P. J. M., Reijnen-Gresnigt M. G., Bloemen R. J. and Van Buul-Offers S. C. (1997) Expression of insulin-like growth factor II (IGF-II) and histological changes in the thymus and spleen of transgenic mice overexpressing IGF-II. Histochem. Cell. Biol. **107:** 193–203

79 Han V. K. M., Matsell D. G., Delhanty P. J. D., Hill D. J., Shimasaki S. and Nygard K. (1996) IGF-binding protein mRNAs in the human fetus: tissue and cellular distribution of developmental expression. Horm. Res. **45:** 160–166
80 Braulke T., Claussen M., Saftig P., Wendland M., Neifer K., Schmidt B. et al. (1995) Proteolysis of IGFBPs by cathepsin D in vitro and in cathepsin D-deficient mice. Prog. Growth Factor Res. **6:** 265–271
81 Nagy E. and Berczi I. (1978) Immunodeficiency in hypophysectomized rats. Acta Endocrinol. **89:** 530–537
82 Guler H., Zapf J., Scheiwiller E. and Froesch E. R. (1988) Recombinant human insulin-like growth factor I stimulates growth and has distinct effects on organ size in hypophysectomized rats. Proc. Natl. Acad. Sci. USA **85:** 4889–4893
83 Fukushima R., Hato F., Kinoshita Y., Tsuji Y. and Kitano A. (1997) Effect of exogenous growth hormone on in vitro proliferation of thymic lymphocytes from the hypophysectomized rats. Cell. Mol. Biol. **43:** 567–579
84 Sornson M. W., Wu W., Dasen J. S., Flynn S. E., Norman D. J., O'Connell S. M. et al. (1996) Pituitary lineage determination by the prophet of pit-1 homeodomain factor defective in ames dwarfism. Nature **384:** 327–333
85 Van Buul-Offers S. C. (1983) Hormonal and other inherited growth disturbances in mice with special reference to the Snell dwarf mouse. A review. Acta. Endocrinol. **103** (Suppl. 258)**:** 1–47
86 Baroni C. (1967) Thymus, peripheral lymphoid tissues and immunological responsiveness of the pituitary dwarf mouse. Experientia **23/4:** 282–283
87 Duquesnoy R. J. (1972) Immunodeficiency of the thymus-dependent system of the ames dwarf mouse. J. Immunol. **108:** 1578–1590
88 Van Buul-Offers S. C. and Van den Brande J. L. (1982) Cellular growth in several organs of normal and dwarfed Snell mice. Acta Endocrinol. **99:** 141–149
89 Pandian M. R. and Talwar G. P. (1971) Effect of growth hormone on the metabolism of thymus and on the immune response against sheep erythrocytes. J. Exp. Med. **134:** 1095–1113
90 Van Buul-Offers S. C., Ueda I. and Van den Brande J. L. (1986) Biosynthetic somatomedin-C (SM-C/IGF-I) increases the lenght and weight of Snell dwarf mice. Pediatr. Res. **20:** 825–827
91 Pierpaoli W., Baroni C., Fabris N. and Sorkin E. (1969) Hormones and Immunological capacity II reconstitution of antibody production in hormonally deficient mice by somatotropic hormone, thyrotropic hormone and thyroxin. Immunology **16:** 217–230
92 Van Buul-Offers S. C. and Van den Brande J. L. (1982) Cellular growth in organs of dwarf mice during treatment with growth hormone, thyroxine and plasma fractions containing somatomedin activity. Acta Endocrinol. **99:** 150–160
93 Takada Y., Bando H., Miyamoto Y., Kosaka M. and Sano T. (1991) Effect of growth hormone on immune function in normal and hypophysectomized rats. Folia Endocrinol. **67:** 1162–1177
94 Kelley K. W. (1995) Immunologic roles of two metabolic hormones, growth hormone and insulin-like growth factor-I, in aged animals. Nutr. Rev. **53:** S95–S104
95 Bar-Dayan Y. and Small M. (1994) Effect of bovine growth hormone administration on the pattern of thymic involution in mice. Thymus **23:** 95–101
96 Beschorner W. E., Divic J., Pulido H., Yao X., Kenworthy P. and Bruce G. (1991) Enhancement of thymic recovery after cyclosporine by recombinant human growth hormone and insulin-like growth factor I. Transplantation **52:** 879–884
97 Weigent D. A. and Blalock J. E. (1994) Effect of the administration of growth-hormone-producing lymphocytes on weight gain and immune function in dwarf mice. Neuroimmunomodulation **1:** 50–58
98 Pierpaoli W. and Sorkin E. (1968) Hormones and immunologic capacity. 1. Effect of heterologous anti-growth hormone (ASTH) antiserum on thymus and peripheral lympatic tissue in mice. Induction of a wasting syndrome. J. Immunol. **101:** 1036–1043
99 Shea B. T., Hammer R. E. and Brinster R. L. (1987) Growth allometry of the organs in giant transgenic mice. Endocrinology **121:** 1924–1930
100 Cecim M., Bartke A., Yun J. G. and Wagner T. E. (1993) Growth allometry of transgenic mice expressing the mouse metallothionein-I/bovine growth hormone gene. Transgene **1:** 125–132
101 Yamada M., Hato F., Kinoshita Y., Tominaga K. and Tsuji Y. (1994) The indirect participation of growth hormone in the thymocyte proliferation system. Cell. Mol. Biol. **40:** 111–121
102 Siddiqui R. A., McCutcheon S. N., Blair H. T., Mackenzie D. D. S., Morel P. C. H., Breier B. H. et al. (1992) Growth allometry of organs, muscles and bones in mice from lines divergently selected on the basis of plasma insulin-like growth factor-I. Growth Dev. Ageing **56:** 53–60
103 Timsit J., Savino W., Safieh B., Chanson P., Gagnerault M. C., Bach J. F. et al. (1992) Growth hormone and insulin-like growth factor-I stimulate hormonal function and proliferation of thymic epithelial cells. J. Clin. Endocrinol. Metab. **75:** 183–188
104 Tomas F. M., Lemmey A. B., Read L. C. and Ballard F. J. (1996) Superior potency of infused IGF-I analogues which bind poorly to IGF-binding proteins is maintained when administered by injection. J. Endocrinol. **150:** 77–84
105 Lemmey A. B., Martin A. A., Read L. C., Tomas F. M., Owens P. C. and Ballard F. J. (1991) IGF-I and the truncated analogue des-(1–3)IGF-I enhance growth in rats after gut resection. Am. Physiol. Soc. **260:** E213–E219
106 Clark R., Strasser J., McCabe S., Robbins K. and Jardieu P. (1993) Insulin-like growth factor-I stimulation of lymphopoiesis. J. Clin. Invest. **92:** 540–548
107 Binz K., Joller P., Froesch P., Binz H., Zapf J. and Froesch E. R. (1990) Repopulation of the atrophied thymus in diabetic rats by insulin-like growth factor I. Proc. Natl. Acad. Sci. USA **87:** 3690–3694
108 van Buul-Offers S. C., Hoogerbrugge C. M., Branger J., Feijlbrief M. and Van den Brande J. L. (1988) Growth-stimulating effects of somatomedin-/insulin-like peptides in Snell dwarf mice. Horm. Res. **29:** 229–236
109 van Buul-Offers S. C., Reijnen-Gresnigt M. G., Hoogerbrugge C. M., Bloemen R. J., Kuper C. F. and Van den Brande J. L. (1994) Recombinant insulin-like growth factor-II inhibits the growth-stimulating effect of growth hormone on the liver of Snell dwarf mice. Endocrinology **135:** 977–985
110 van Buul-Offers S. C., De Haan K., Reijnen-Gresnigt M. G., Meinsma D., Jansen M., Oei S. L. et al. (1995) Overexpression of human IGF-II in transgenic mice causes increased growth of the thymus. J. Endocrinol. **144:** 491–502
111 Kooijman R., Van Buul-Offers S. C., Scholtens L. E., Reijnen-Gresnigt R. G. and Zegers B. J. M. (1997) T and B cell development in pituitary deficient insulin-like growth factor-II transgenic dwarf mice. J. Endocrinol. **155:** 165–170
112 Kooijman R., Van Buul-Offers S. C., Scholtens L. E., Schuurman H-J., Van den Brande J. L. and Zegers B. J. M. (1995) T cell development in insulin-like growth factor-II transgenic mice. J. Immunol. **15:** 5736–5745
113 Koster J. G., Reijnen-Gresnigt M. G., Bloemen R. J., Stegeman B. I. and Van Buul-Offers S. C. (1996) Differences in growth regulation by IGF-II and IGFBP3 in lymphoid tissues of IGF-II transgenic mice. 10th International Congress of Endocrinology, San Francisco, CA, P2-253
114 Ward A., Bates P., Fisher R., Richardson L. and Graham C. F. (1994) Disproportionate growth in mice with Igf-2 transgenes. Proc. Natl. Acad. Sci. USA **91:** 10365–10369
115 Rogler C. E., Yang D., Rossetti L., Donohoe J., Alt E., Chang C. J. et al. (1994) Altered body composition and increased frequency of diverse malignancies in insulin-like growth factor-II transgenic mice. J. Biol. Chem. **269:** 13779–13784
116 Wolf E., Kramer R., Blum W. F., Foell J. and Brem G. (1994) Consequences of postnatally elevated insulin-like growth factor-II in transgenic mice: endocrine changes and effects on body and organ growth. Endocrinology **135:** 1877–1886

117 Badolato R., Bond H. M., Valerio G., Petrella A. A., Morrone G., Waters M. J. et al. (1994) Differential expression of surface membrane growth hormone receptor on human peripheral blood lymphocytes detected by dual fluorochrome flow cytometry. J. Clin. Endocrinol. Metab. **799:** 984–990

118 Gelato M. C. (1996) Aging and immune function: a possible role for growth hormone. Horm. Res. **45:** 46–49

119 Kooijman R., Willems M., de Haas C. J. C., Rijkers G. T., Schuurmans A. L. G., Van Buul-Offers S. C. et al. (1992) Expression of type I insulin-like growth factor receptors on human peripheral blood mononuclear cells. Endocrinology **131:** 2244–2250

120 Federici M., Porzio O., Zucaro L., Fusco A., Borboni P., Lauro D. et al. (1997) Distribution of insulin/insulin-like growth factor-I hybrid receptors in human tissues. Mol. Cell. Endocrinol. **129:** 121–126

121 Bailyes E. M., Nave B. T., Soos M. A., Orr S. R., Hayward A. C. and Siddle K. (1997) Insulin receptor/IGF-1 receptor hybrids are widely distributed in mammalian tissues: quantification of individual receptor species by selective immunoprecipitation and immunoblotting. Biochem. J. **327:** 209–215

122 Lee P. D. K., Rosenfeld R. G., Hintz R. L. and Smith S. D. (1986) Characterization of insulin, insulin-like growth factors I and II, and growth hormone receptors on human leukemic lymphoblasts. J. Clin. Endocrinol. Metab. **62:** 28–35

123 Weigent D. A., Baxter J. B. and Blalock J. E. (1992) The production of growth hormone and insulin-like growth factor-I by the same subpopulation of rat mononuclear leukocytes. Brain Behav. Immun. **6:** 365–376

124 Varma S., Sabharwal P., Sheridan J. F. and Malarkey W. B. (1993) Growth hormone secretion by human perpheral blood monocuclear cells detected by an enzyme-linked immunoplague assay. J. Clin. Endocrinol. Metab. **76:** 49–53

125 Baxter J. B., Blalock J. E. and Weigent D. A. (1991) Characterization of immunoreactive insulin-like growth factor-I from leukocytes and its regulation by growth hormone. Endocrinology **129:** 1727–1734

126 Arkins S., Rebeiz N., Biragyn A., Reese D. L. and Kelley K. W. (1993) Murine macrophages express abundant insulin-like growth factor-I Class I Ea and Eb transcripts. Endocrinology **133:** 2334–2343

127 D'Ercole A. J., Stiles A. D. and Underwood L. E. (1984) Tissue concentrations of somatomedin C: further evidence for multiple sites of synthesis and paracrine or autocrine mechanisms of action. Proc. Natl. Acad. Sci. USA **81:** 935–939

128 Hansson H. A., Nilsson A., Isgaard J., Billig H., Isaksson O., Skottner A. et al. (1988) Immunohistochemical localization of insulin-like growth factor I in the adult rat. Histochemistry **89:** 403–410

129 Murphy L. J., Bell G. I. and Friesen H. G. (1987) Tissue distribution of insulin-like growth factor I and II messenger ribonucleic acid in the adult rat. Endocrinology **120:** 1279–1282

130 Nyman T. and Pekonen F. (1993) The expression of insulin-like growth factors and their binding proteins in normal human lymphocytes. Acta Endocrinol. **128:** 168–172

131 Merimee T. J., Grant M. B., Broder C. M. and Cavalli-Sforza L. L. (1989) Insulin-like growth factor secretion by human B-lymphocytes: a comparison of cells from normal and pygmy subjects. J. Clin. Endocrinol. Metab. **69:** 978–984

132 Weigent D. A., Blalock J. E. and LeBoeuf R. D. (1991) An antisense oligodeoxynucleotide to growth hormone messenger ribonucleic acid inhibits lymphocyte proliferation. Endocrinology **128:** 2053–2057

133 Villanua M. A., Szary A., Bartke A. and Esquifino A. I. (1992) Changes in lymphoid organs of Ames dwarf mice after treatment with growth hormone, prolactin or ectopic pituitary transplants. J. Endocrinol. Invest. **15:** 587–595

134 Dumont F., Robert F. and Bischoff P. (1979) T and B lymphocytes in pituitary dwarf Snell-Bagg mice. Immunology **38:** 23–31

135 Fabris N., Pierpaoli W. and Sorkin E. (1971) Hormones and the immunological capacity. IV. Restorative effects of developmental hormones or of lymphocytes on the immunodeficiency syndrome of the dwarf mouse. Clin. Exp. Immunol. **9:** 227–240

136 Thissen J. P., Underwood L. E., Maiter D., Maes M., Clemmons D. R. and Ketelslegers J. M. (1991) Failure of insulin-like growth factor-I (IGF-I) infusion to promote growth in protein-restricted rats despite normalization of serum IGF-I concentrations. Endocrinology **128:** 885–890

137 Conlon M. A., Francis G. L., Tomas F. M., Wallace J. C., Howarth G. S. and Ballard F. J. (1995) Continuous 14 day infusion of IGF-II increases the growth of normal female rats, but exhibits a lower potency than IGF-I. J. Endocrinol. **144:** 91–98

138 Wanke R., Hermanns W., Folger S., Wolf E. and Brem G. (1991) Accelerated growth and visceral lesions in transgenic mice expressing foreign genes of the growth hormone family: an overview. Pediatr. Nephrol. **5:** 513–521

139 Wanke R., Wolf E., Hermanns W., Folger S., Buchmueller T. and Brem G. (1992) The GH-transgenic mouse as an experimental model for growth research: clinical and pathological studies. Horm. Res. **37:** 74–87

140 Gruaz N. M., D'Alleves V., Charnay Y., Skottner A., Ekvaern S., Fryklund L. et al. (1997) Effects of constant infusion with insulin-like growth factor-I (IGF-I) to immature female rats on body weight gain, tissue growth, and sexual function – evidence that such treatment does not affect sexual maturation or fertility. Endocrine **6:** 11–19

141 Mathews L. S., Hammer R. E., Behringer R. R., D'Ercole A. J., Bell G. I., Brinster R. L. et al. (1988) Growth enhancement of transgenic mice expressing human insulin-like growth factor I. Endocrinology **123:** 2827–2833

142 Quaife C. J., Mathews L. S., Pinkert C. A., Hammer R. E., Brinster R. L. and Palmiter R. D. (1989) Histopathology associated with elevated levels of growth hormone and insulin-like growth factor I in transgenic mice. Endocrinology **124:** 40–48

143 Backeljauw P. F., Underwood L. E., Miras M., Arriazu M. C., Heinrich J., Ghizzoni L. et al. (1996) Prolonged treatment with recombinant insulin-like growth factor-I in children with growth hormone insensitivity syndrome – a clinical research center study. J. Clin. Endocrinol. Metab. **81:** 3312–3317

144 Jardieu P., Clark R., Mortensen D. and Dorshkind K. (1994) In vivo administration of insulin-like growth factor-I stimulates primary B lymphopoiesis and enhances lymphocyte recovery after bone marrow transplantation. J. Immunol. **152:** 4320–4327

145 LeRoith D., Yanowski J., Kaldjian E. P., Jaffe E. S., LeRoith T., Purdue K. et al. (1996) The effects of growth hormone and insulin-like growth factor I on the immune system of aged female monkeys. Endocrinology **137:** 1071–1079

146 Montecino-Rodriguez E., Clark R., Johnson A., Collins L. and Dorshkind K. (1996) Defective B cell development in Snell dwarf (dw/dw) mice can be corrected by thyroxine treatment. J. Immunol. **157:** 3334–3340

147 Gala R. R. (1995) Influence of thyroxine and thyroxine with growth hormone and prolactin on splenocyte subsets and on the expression of interleukin-2 and prolactin receptors on splenocyte subsets of Snell dwarf mice. Proc. Soc. Exp. Biol. Med. **210:** 117–125

148 Murphy L. J., Molnar P., Lu X. and Huang H. (1995) Expression of human insulin-like growth factor-binding protein-3 in transgenic mice. J. Mol. Endocrinol. **15:** 293–303

149 Murphy L. J., Rajkumar K. and Molnar P. (1995) Phenotypic manifestations of insulin-like growth factor binding protein-1 (IGFBP-1) and IGFBP-3 overexpression in transgenic mice. Prog. Growth Factor Res. **6:** 425–432

150 Pintar J. E., Cerro J. A. and Wood T. L. (1996) Genetic approaches to the function of insulin like growth factor-binding proteins during rodent development. Horm. Res. **45:** 172–177

151 Dai J. and Baxter R. C. (1994) Regulation in vivo of the acid-labile subunit of the rat serum insulin-like growth factor-binding protein complex. Endocrinology **135:** 2335–2341

152 Duquesnoy R. J., Kalpaktsoglou P. K. and Good R. A. (1970) Immunological studies of the Snell-Bagg pituitary dwarf mouse. Proc. Soc. Exp. Biol. Med. **133:** 201–206
153 Robbins K., McCabe S., Scheiner T., Strasser J., Clark R. and Jardieu P. (1994) Immunological effects of insulin-like growth factor-I-Enhancement of immunoglobulin synthesis. Clin. Exp. Immunol. **95:** 337–342
154 Nagy E., Berczi I. and Friesen H. G. (1983) Regulation of immunity in rats by lactogenic and growth hormones. Acta Endocrinol. **102:** 351–357
155 Wit J. M., Kooijman R., Rijkers G. T. and Zegers B. J. M. (1993) Immunological findings in growth hormone-treated patients. Horm. Res. **39:** 107–110
156 Geffner M. (1997) Effects of growth hormone and insulin-like growth factor I on T-and B-lymphocytes and immune function. Acta Paediatr. **86:** 76–79
157 Kirstein M., Aston C., Hintz R. and Vlassara H. (1992) Receptor-specific induction of insulin-like growth factor-I in human monocytes by advanced glycosylation and product-modified proteins. J. Clin. Invest. **90:** 439–446
158 Arkins S., Rebeiz N., Brunke-Reese D. L., Biragyn A. and Kelley K. W. (1995) Interferon-gamma inhibits macrophage insulin-like growth factor-I synthesis at the transcriptional level. Mol. Endocrinol. **9:** 350–360
159 Kooijman R., Malur A., Van Buul-Offers S. C. and Hooghe-Peters E. L. (1997) Growth hormone expression in murine bone marrow cells is independent of the pituitary transcription factor Pit-1. Endocrinology **138:** 3949–3955
160 De Benedetti F., Alonzi T., Moretta A., Lazzaro D., Costa P., Poli V. et al. (1997) Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I – a model for stunted growth in children with chronic inflammation. J. Clin. Invest. **99:** 643–650