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Insulin-Like Growth Factor-1 Physiology: Lessons from Mouse Models

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Introduction

Insulin-like growth factor-1 (IGF-1) belongs to a small family of secreted single chain polypeptides that play important roles in growth, development, and metabolism. This family includes proinsulin, insulin, IGF-1, and IGF-2, which show high amino acid sequence homology and share similar ternary structure. IGF-1 and IGF-2 are derived from 2 separate genes and transcribed by virtually all cells. Because these factors play pivotal roles in cellular proliferation, differentiation, and function, they are tightly regulated at the transcriptional and posttranscriptional levels.

IGF-1 acts in an autocrine/paracrine and endocrine modes and is therefore secreted to the serum and delivered to distant tissues. Hepatocytes are the major source of secreted IGF-1, producing 75% of serum IGF-1.¹ In the liver *igf-1* gene expression is regulated mainly by pituitary gland-derived growth hormone (GH), although nutrition and insulin also affect its expression.² In turn, endocrine/serum IGF-1 regulates pituitary GH production through a negative feedback loop.² In extrahepatic tissues, *igf-1* gene expression is regulated by tissue-specific factors or by GH.² *Igf-2* gene expression is GH-independent and is tightly regulated by parental imprinting.³ In humans, *igf-1* and *igf-2* genes are expressed throughout life. However, although serum IGF-1 levels decrease after puberty, IGF-2 levels in serum remain high throughout adulthood and are 3.5-fold higher than IGF-1 levels.² In contrast, in rodents, IGF-2 is transcribed predominantly during fetal growth and its expression in the adult animal is hardly detectable, whereas IGF-1 is the major circulating ligand and does not decline in the adult animal.

The effects of IGF-1 and IGF-2 on cellular behavior are mediated by the type 1 IGF receptor (IGF-1R), which conveys survival and mitogenic signals to the cell through a complex

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network of signaling mechanisms.³ The IGF-1R is a membrane-bound tyrosine kinase heterotetramer. The intracellular domains convey adenosine triphosphate binding sites and are able to autophosphorylate tyrosine residues, which serve as the docking site for intracellular proteins, important for signal transduction.

IGF-1R shares 60% homology with the insulin receptors A and B (IR-A, IR-B) but differs in ligand specificity and affinity as well as in transmission of downstream signals.⁴ Because both the IGF-1R and IR are closely related, they can form hybrid heterodimeric receptors consisting each of an insulin and IGF-IR α - β dimer, which mediate mainly IGF signaling.⁴ The role of the hybrid receptors is not fully understood.

Binding of the IGFs to the IGF-1R results in autophosphorylation of tyrosines on the intracellular portion of the β -subunit. The phosphorylated tyrosines serve as docking sites for several substrates, including the IR substrates (IRS) 1 to 4 and Shc, which initiate phosphorylation cascades. IRS-1 activates the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3-K), leading to subsequent increase in membrane-bound phospholipid phosphatidylinositol-3, 4, 5-triphosphate and the recruitment of phosphoinositide-dependent kinase 1 and Akt (or protein kinase B) to the membrane. There are 3 central effectors to the downstream signaling events triggered by Akt: the mammalian target of rapamycin (mTOR) complex 1 (mTORC1), forkhead transcription factors (FOXO), and glycogen synthase kinase 3 (GSK3). Activation of mTORC1 plays an important role in cell growth and survival by promoting nutrient uptake, storage of energy, and protein translation. This pathway has also been associated with IGF-1-mediated cell survival, proliferation, hypertrophy, and cell migration.⁵⁻⁷ The FOXO proteins promote cell cycle arrest, apoptosis, oxidative stress, and the activation of gluconeogenic enzymes. Their phosphorylation and cytoplasmic retention is mediated by Akt and implicated in IGF-I-induced cell proliferation, survival, and hypertrophy.^{6,8-10} The GSK3 protein, which is inhibited by Akt, increases glycogenesis and is also involved in the Wnt signaling pathway. Studies also suggest that GSK3 is involved in IGF-I-induced antiapoptotic and hypertrophic effects.^{6,11,12} Apart from these pathways, Akt can also promote cell survival via the inactivating phosphorylation of the apoptotic protein Bad, and procaspase 9.^{13,14}

The bioactivity of IGF is modulated by IGF-binding proteins (IGFBPs), which facilitate their stability in serum and extracellular matrices.^{15,16} To date, 6 high-affinity IGFBPs have been characterized.^{15,16} The expression and distribution of the IGFBPs are tissue dependent and modified with exercise,¹⁷ surgery, pregnancy,¹⁸ nutrition,¹⁹ and aging.²⁰ During intrauterine growth, IGFs are found in binary complexes with IGFBPs, in which IGFBP-2 is the predominant binding protein in serum. However, during postnatal growth, 85% of the IGF pool is found in ternary complexes with IGFBP-3 and the acid-labile subunit (ALS), a protein that further stabilizes IGFs in serum.^{15,16} Only a few (5%) of the IGFs are found free in serum and their roles are yet unclear. At target tissues, IGFBPs can either reduce or facilitate IGF-1 bioactivity.^{15,16} On one hand, IGFBPs can limit access of IGF-1 to cell-surface IGF-1R, because IGFBPs have higher affinity for IGF-1 than the receptor. On the other hand, IGFBPs can act as reservoirs that slowly release the IGFs, allowing prolonged IGF action in local microenvironments. It has been reported that some IGFBPs have IGF-1-independent effects on cells.^{15,16}

IGF-1 System in Normal Physiology

IGF-1 plays a pivotal role in fetal development, adolescent growth, and adult tissue homeostasis. Together with insulin and GH, IGFs regulate glucose and lipid metabolism, and thereby regulate body composition. Imbalance in IGF production or function is associated with various pathologic conditions, including short stature, insufficient skeletal acquisition, alterations in body composition (lean and fat mass), impairments in reproduction, reduced mental and physical capacity associated with aging, and metabolic disorders. With the development of gene-targeting approaches in animals in the last 2 decades, the roles of the IGF system in normal physiology and disease have become more explicable. The next sections review the effects of the IGF system on musculoskeletal development, reproduction, metabolism, and longevity, as learned from mouse models of IGFs.

Body Size

Animal models of IGF deficiency have confirmed its critical role in embryogenesis and postnatal growth. IGF-1 null mice show marked growth retardation in utero and postnatally. These mice are 65% of normal weight at birth and most die shortly after birth.^{21–23} Survivors do not undergo a peripubertal growth spurt and have only 30% of the body weight of wild-type animals as adults. IGF-2 null mice are also growth impaired but their growth retardation occurs exclusively in utero, whereas their postnatal growth is normal,²¹ indicating that in mice only IGF-1 is critical postnatally. Likewise, IGF-1 receptor null mice weigh 55% of wild-type littermates and die within a few hours after birth because of respiratory failure. These mice show organ hypoplasia,²¹ lung, skin, bone, and neurologic defects.^{21,23} Taken together, the IGF-1R null mice established this receptor as an essential regulator of organogenesis. Contrary to models of IGF deficiency, IGF-1 transgenic mice showed significant increases in body weight and organomegaly caused by tissue hyperplasia.

Studies in mice lacking the different IGFBPs show modest deficiencies in somatic growth (10%–20% decreases in body weight), mostly attributed to decreased IGF levels in serum and decreases in IGF stability in tissues. A triple knockout of IGFBP-3, IGFBP-4, and IGFBP-5, the main IGFBPs present in serum, resulted in only 22% reductions in body weight, despite 65% decreases in serum IGF-1 levels.²⁴ Similarly, gene inactivation of the ALS, which stabilizes the binary complex of IGF-1 and IGFBP-3 or IGFBP-5, resulted in a ~10% to 20% decrease in body weight.^{25,26} Reduced IGF-1 bioavailability was reported in transgenic mice with ubiquitous expression of IGFBPs and the ALS. Overexpression of ALS resulted in reduced body weight gains during the first 3 weeks of growth and significantly reduced body weights through puberty.²⁷ Global overexpression of IGFBP-1, IGFBP-2, IGFBP-3, or IGFBP-5 also resulted in growth retardation.^{24,28–32} A study published by Stratikopoulos and colleagues³³ showed that serum IGF-1 contributes to approximately 30% of the adult body size; therefore the inhibitory effect seen in the IGFBP transgenic mice likely result from inhibition of IGF action in both serum and tissues.

In conjunction with IGF mutagenesis studies, 2 IGF analogues that have a significant reduction in affinity for the IGFBPs but retain normal affinity for the IGF-1 receptor were described: R3-IGF-1^{34–36} and Des1-3-IGF-1.^{37–40} The R3-IGF-1 mutant has a Glu to Arg

substitution at position 3 of the IGF-1 peptide and the Des1-3-IGF-1, has a 3 amino acid truncation at the amino terminus. Both mutants have several times lower affinity to IGFBP-3 than native IGF-1 and show greatly reduced binding to all other IGFBPs.^{41–44} Introduction of these 2 mutations to mouse models via knockin resulted in enhanced somatic growth, which was attributed to increased IGF-1 bioavailability in tissues.^{45,46} Together, studies of IGFBP knockout and the Des/R3 knockin mouse models support the notion that IGFBPs serve as reservoirs that release and control IGF action in tissues.

Skeletal Acquisition

Growth of long bones occurs at the growth plate, which is a highly complex, spatially polarized structure. GH and IGF-1 regulate longitudinal bone growth via their action on chondrocytes within the growth plate.⁴⁷ Excess of GH or IGF accelerates chondrogenesis, enhances linear growth, and inactivates mutations in the GH, IGF, or the GH receptor (GHR), in both human and animal models, retard linear bone growth.⁴⁸ In Snell dwarf (dw/dw) mice, deletion of the *pit-1* transcription factor resulted in a loss of GH production and reduced bone length as a result of reductions in cartilage hypertrophy and delayed epiphyseal ossification.^{49–51} Likewise, in the Ames dwarf mouse (dt/dt), deletion of the *prop-1*, an upstream regulator of *pit-1*, resulted in reductions in lean mass, bone area, and bone mineral content.^{52,53} GH binds to its receptor, the GHR, which mediates its effects via the Janus kinase/signal transducer and activator of transcription 5 (STAT5) pathway. Ablation of STAT5 in mice led to reduced bone length in a manner similar to Ames and Snell dwarf mice, although this effect was mainly apparent in male mice.⁵⁴ Similarly, total inactivation of the *igf-1* gene resulted in a severe bone phenotype with shortened femoral length, increased chondrocyte apoptosis, and 25% reduction in cortical bone size.⁵⁵ IGF-1 actions on the skeleton are mediated via the IGF-1R, the main effectors of which are the insulin-receptor substrate 1 and 2 (IRS-1, IRS-2). IRS-1 or IRS-2 null mice showed growth retardation, low bone mineral density (BMD), reduced cortical and trabecular thickness, and low bone formation rates.⁵⁶

Skeletal acquisition depends not only on the total levels of IGF-1 but also on its bioavailability. Overexpression of the different IGFBPs^{24,28–32} or the ALS protein²⁷ resulted in decreases in cortical bone density, cortical bone volume, cortical thickness, and decreases in cancellous bone. Ablation of IGFBP-2⁵⁷ or IGFBP-4,²⁴ or the ALS protein,²⁵ also resulted in osteopenic phenotype, likely because of increases in IGF-1 degradation and consequent reductions in its bioavailability.

IGF-1 exerts its effects on skeletal acquisition in an endocrine and autocrine/para-crine manner. Studies from inbred mouse strains showed correlations between serum IGF-1 levels and skeletal acquisition. Mouse strains with low IGF-1 (C57BL/6J) have reduced total BMD and cortical thickness, whereas mice with higher serum IGF-1 levels (C3H/HeJ) show increased total BMD and femoral cortical thickness.⁵⁸ In addition, congenic mice (B6.C3H.6T) with a 40% reduction in serum IGF-I also had reduced BMD and delayed development.⁵⁹ We have generated a mouse model in which the *igf-1* gene was ablated specifically in the liver.⁶⁰ Liver IGF-1-deficient (LID) mice had 75% decreases in serum IGF-1 levels, with minor decreases (~5%) in body length. Skeletal characterization of the

LID mice throughout development revealed no alterations in cancellous bone, but significant decreases in femoral total area and cortical area, resulting in slender bones with reduced stiffness and reduced strength in bending.⁶¹ Thus, reductions in serum IGF-1 tended to target cortical bone by preventing periosteal apposition during growth. Marrow area was not altered during early growth and decreased relative to controls from 16 to 32 weeks of age (endosteal infilling). In contrast, increased IGF-1 levels in serum in mice expressing hepatocyte-specific rat IGF-1 transgene (HIT) led to increases in body weight, body length, and femoral length, as well as femoral total area, cortical area, cortical thickness, and robustness.^{45,46}

To better understand the role of IGF-1 in bone accrual and maintenance, a tissue-specific gene-targeting approach was used. Ablation of the *igf-1* gene in chondrocytes resulted in significant reductions in body weight, body length, total BMD, and femoral width and length beginning at 4 weeks of age in both genders.⁶² Similarly, conditional deletion of IGF-1 in cells expressing type 1 α_2 collagen (skeletal muscle and bone) resulted in 35% reductions in body weight, and ~20% reductions in femur areal BMD.⁶³ In addition, mineralization was reduced starting at embryonic development as a result of impaired osteoblast function.⁶³ Tissue-specific modulation of IGF-1 action was also achieved by expression of IGFBPs. IGFBP-4 overexpression in osteoblasts resulted in decreased femoral cortical density, cortical thickness, and periosteal circumference in both genders.⁶⁴ Mice expressing IGFBP-5 under the osteocalcin promoter showed decreased BMD, trabecular bone volume, and bone formation as well as mineralization defects indicated by a reduced mineral/matrix ratio in cortical bone and reduced collagen maturity in secondary ossification centers.⁶⁵ Because IGF-1 exerts its effects in an endocrine and autocrine/paracrine manner, to better understand its role in osteoblast and osteoclast function, it was necessary to ablate the IGF-1 receptor (rather than the ligand) in a cell-specific manner, to avoid its activation regardless of the IGF-1 source. When IGF-1 receptor was disrupted specifically in osteoblasts, no alterations in body size or femoral length were noted, but matrix mineralization was impaired, as shown by increased osteoid volume and osteoid surface.⁶⁶ This study was crucial to establishing the role of IGF-1 in bone mineralization. In contrast, increased expression of IGF-1 specifically in osteoblasts increased femur length, cortical width, and cross-sectional area and enhanced bone formation and mineralization.⁶⁷

Animal models have established that IGF-1 has a fundamental role in determination of bone accrual.⁶⁸ We now know that loss of serum IGF-1 affects mainly postpubertal bone accrual. Specifically, serum IGF-1 regulates transversal bone growth and periosteal bone apposition. In contrast, loss of tissue IGF-1 affects early postnatal and prepubertal growth. These studies also showed that the IGF-1 axis in osteoblasts is a strong regulator of bone mineralization.

Muscle Gain and Maintenance

IGF-1 and IGF-2 play key roles in skeletal muscle accrual during development, muscle maintenance, and aging, as well as during muscle injury. Mice deficient in IGF-2 or the IGF-1R show muscle hypoplasia, whereas mice with transgenic IGF-1 expression specifically in muscle display increased muscle mass and enhanced muscle strength.⁶⁹ Accordingly, mice that overexpress a skeletal-muscle-specific, dominant negative IGF-1R

(MKR mice) have impaired muscle growth, reduced fiber cross-sectional area, and muscle wet weights, relative to control mice.⁷⁰

In vivo studies have shown that IGF-1-induced muscle hypertrophy results from activation and proliferation of muscle satellite cells. IGFs ameliorated the aging/dystrophic muscle phenotype of the *mdx* mice,⁷¹ likely because of increased satellite cell proliferation. Furthermore, in aged mice overexpressing IGF-1, centralized nuclei expressing neonatal myosin heavy chain (an indication of regenerating myofibers) have been identified.⁷² The roles of IGF-1 in regulation of cell cycle have been established in various cell lines. Studies have shown that IGF-1 stimulates progression from G1 to S phase via downregulation of the p27Kip1 inhibitor. Accordingly, satellite cells harvested from the muscle of transgenic mice overexpressing IGF-1 under the α -actin promoter showed a 5-fold increase in proliferative capacity, relative to that of controls.⁷³ Furthermore, administration of IGF-1 to muscle of aged mice inhibited p27Kip1 in satellite cells.⁷³

The cellular and molecular mechanisms by which IGFs facilitate muscle growth, differentiation, and maintenance were shown in experimental systems of muscle regeneration. After acute muscle injury, local IGF-1 production is increased (with no alterations in systemic IGF-1 levels) and promotes muscle repair via stimulation of myogenic cell proliferation and survival through activation of the phosphatidylinositol 3-kinase (PI3K) and the mitogen-activated protein kinase (MAPK) pathways.⁷⁴ In addition, IGF-1 promotes nerve sprouting and has a protective effect against nerve degeneration.^{75–78} Thus, improved outcomes of IGF-1-induced muscle regeneration may also result from its effects on muscle reinnervation during the repair process. Likewise, aged mice treated with IGF-1 have thicker neurons with increased branches compared with those of aged controls.⁷⁹

Paradoxically, IGF stimulates two mutually exclusive cellular responses, namely mitogenesis and myogenesis (differentiation), through activation of the IGF-1R. The intuitive question that arises is: how do cells select their response to IGF signal? A recent study with primary myocytes and the C2C12 muscle cell line showed that IGF-1 mediates different cellular responses under normoxic and hypoxic conditions.⁸⁰ Under normoxia, IGF activates the Akt-mTOR, p38, and extracellular signal-regulated kinase (Erk1/2) MAPK pathways. However, hypoxia suppresses basal and IGF-induced Akt-mTOR and p38 activity and enhances and prolongs IGF-induced Erk1/2 activation in a hypoxia-inducible factor 1-dependent fashion. This finding implies that during acute injury and hypoxic conditions, IGF-1 induces satellite cell proliferation, an early response important in the regenerative process. Physiologically, it is suggested that cells integrate IGF-1R activation with oxygen availability and respond accordingly.

IGF-1 in muscle plays a critical in promoting hypertrophy as well as in the response to muscle damage and subsequent regeneration. IGF-1 signals to both satellite cells and myofibers, and its distinct effects in muscle likely depend on oxygen tension.

Reproduction

Female reproduction in mammals is a complex process, which involves many developmental steps and cell-cell communication. Endocrine, paracrine, and autocrine action of steroid

hormones and growth factors from systemic or local origin coordinate the primary follicle, preantral, and antral follicle development and ovulation.⁸¹ IGF-1 plays an important role in cellular differentiation and reproductive function.⁸²

Studies in animal models have shown that IGFs and insulin augment the action of gonadotropins in the control of ovarian steroidogenesis and follicular maturation. In synergy with gonadotropins and other growth factor families such as TGF (transforming growth factor) superfamily members, the IGF system participates in the selection of the dominant follicle⁸³ and subsequent development into the Graafian follicle,^{84–86} as well as in the processes of ovulation,⁸⁷ corpus luteum formation,⁸⁸ and atresia of nondominant follicles.⁸⁹ Animal studies have shown the interaction between intraovarian/intrafollicular IGF system and follicle-stimulating hormone (FSH) action in granulosa cells. IGF-1 regulates antrum formation and synergizes FSH action by increasing the aromatase activity in granulosa cells.^{90–93}

IGF-1 is selectively expressed in the granulosa cells of developing follicles and is critical for normal reproductive function in mice,^{94,95} whereas the IGF-1R is expressed in both the granulosa cells and in oocytes of murine and human follicles, suggesting a potential paracrine action of IGF-1.^{93,96} IGF-1 stimulates the proliferation and differentiation of granulosa cells⁹⁷ and promotes maturation of follicles and denuded human and mouse oocytes in vitro.⁹⁸ Ablation of the *igf-1* -gene in mice leads to infertility characterized by follicular arrest at the late preantral stage,^{93,99} suggesting an essential role of IGF-1 during folliculogenesis.

IGF bioavailability in the ovary is regulated by IGFBPs,¹⁰⁰ which have inhibitory roles in regulating IGF-1 actions.^{101–103} Mice overexpressing the IGFBP-1 under the control of the α 1-antitrypsin promoter show reduced ovulation rate, possibly associated with impairment in IGF-1 action on follicular cells as well as altered gonadotropin-releasing hormone and luteinizing hormone (LH) secretions.¹⁰¹ In addition, transgenic mice that overexpress IGFBP-5,¹⁰³ IGFBP-3¹⁰² driven by the mouse phosphoglycerate kinase I, or the cytomegalovirus (CMV) promoters show reduced litter size. Likewise, transgenic mice that overexpress the ALS driven by CMV promoter show significant reductions in litter size,²⁷ likely as a result of sequestration of IGF-1 and severe reductions in its bioavailability. Knockout of the pregnancy-associated plasma protein-A, a metallo-protease that cleaves the IGFBP4 in the ovary, showed an overall reduction in litter size, reduced number of ovulated oocytes, and reduced expression of ovarian steroidogenic enzyme.¹⁰⁴

IGF and insulin signaling pathways in the central nervous system (CNS) have been also implicated in female reproductive function, and specific ablation of their cognitive receptors (in nestin-positive cells) showed impaired follicular maturation, likely because of hypothalamic dysregulation of LH.¹⁰⁵ However, oocyte-specific ablation of the IR, IGF-1R, or both⁹⁸ showed normal female reproductive functions reflected by normal estrous cyclicity, oocyte development and maturation, parturition frequency, and litter size. IGF-1 and IRs in the CNS regulate the gonadotroph axis, whereas in the ovary their presence in granulosa cells plays a major role in oocyte function. Studies have suggested that intrafollicular IGF-1 is a determinant of follicular selection and dominance, and it is the net

bioavailability of intrafollicular IGF-1 that may distinguish follicles destined to ovulate from those that succumb to atresia.^{85,93}

Metabolic Homeostasis

Insulin is the principle regulator of carbohydrate and lipid metabolism.¹⁰⁶ However, its interactions with the GH/IGF axis also contribute to metabolic homeostasis. The interplay between GH and insulin is well documented⁴⁸ and is not within the scope of this review. GH antagonizes insulin action in liver and peripheral tissues, and it increases hepatic glucose production via stimulation of gluconeogenesis and glycogenolysis. Moreover, GH decreases glucose uptake by muscle, and stimulates lipolysis and free fatty acid secretion, which subsequently antagonize insulin action. In animal models with reduced IGF-1 in serum, such as the LID mice, GH is increased because of an impaired negative feedback at the level of the pituitary, leading to hyperinsulinemia, deterioration of insulin action, and impaired carbohydrate metabolism.^{107,108}

In the early 1990s, with the availability of recombinant IGF-1, various groups studied the potency of recombinant IGF-1 to cure patients with severe insulin resistance.¹⁰⁹ These studies showed that a bolus injection of recombinant IGF-1 could reduce both insulin and blood glucose levels. IGF-1 therapy lasted for 1 to 16 months,^{110–114} and although it consistently reduced glucose and insulin levels, the very high doses of IGF-1 caused adverse complications such as muscle pain, fluid retention, benign intracranial hypertension, and worsening retinopathy. Also, because of the tight regulation of the GH/IGF-1 axis, interpretation of the results from these studies is difficult because, in addition to its insulin-like effects, IGF-1 also inhibits GH secretion. Yet, with the development of tissue-specific gene targeting, we were able to show that in a mouse model with decreased serum IGF-1 and increased GH (LID mouse), inhibition of GH restored insulin sensitivity, suggesting that GH (and not IGF-1) plays a major role in modulating insulin action.^{107,108} In addition, in a mouse model with 2-fold to 3-fold increases in serum IGF-1 levels (HIT mice), in which GH levels were similar to those of control mice, we found that insulin sensitivity was not enhanced but was comparable with controls.¹¹⁵ Nonetheless, in a clinical study with acromegalic patients treated with a GH antagonist (pegvisomant), insulin sensitivity was improved, but further improvement was observed when a combined treatment of pegvisomant and IGF-1 was given,¹¹⁶ suggesting that IGF-1 exerts additional effects on insulin sensitivity that are not mediated by suppression of GH secretion.

IGF-1R is not expressed in adult liver or adipose tissue and therefore IGF-1-mediated metabolic effects originate from other insulin-responsive tissues. Likewise, disruption of the IGF-1R in β cells resulted in a defect in insulin secretion and subsequent insulin resistance.^{117,118} Similarly, IGF-1 plays important roles in the central control of peripheral metabolism. Intracerebroventricular infusion of exogenous IGF-1 increases liver sensitivity to insulin.¹¹⁹ Nonetheless, neuronal-specific IGF-1R inactivation in mice shows no metabolic phenotype, but showed low serum GH levels.¹²⁰ Muscle-specific IGF-1R inactivation did not result in metabolic phenotype, although inactivation of cardiac IGF-1R resulted in impaired exercise-induced cardiac hypertrophy.¹²¹ However, inactivation of both

IGF-1R and IRs in muscle via overexpression of a dominant negative IGF-1R resulted in adverse insulin resistance and diabetes.¹²²

Insulin, GH, and IGF-1 cointeract to establish controlled carbohydrate and lipid metabolism. IGF-1 has insulin-like effects when given exogenously in high concentrations. However, the role of physiologic IGF-1 is less clear because of its tight regulation by GH.

Insulin/IGF-1 Signaling and the Health Span

One of the most paradoxical recent developments in insulin and IGF-1 signaling (IIS) research has been observations that reduction in IIS extends life span. Studies in *Caenorhabditis elegans* indicate that down-mutations in *daf2* and *AGE*, which encode orthologs of the mammalian insulin/IGF-1 receptor and PI3K, respectively, extend life span. Moreover, inactivating mutations in *daf16*, which encode an ortholog of the mammalian FOXO transcription factor, prevent *daf2* and *AGE* mutants from extending life span. PI3K normally phosphorylates and inhibits the activity of FOXO, which promotes the transcription of genes mediating resistance to stress, such as super-oxide dismutase, thus providing a mechanistic explanation of how reduced IIS could increase health span.¹²³ Similar findings have been made in the other major invertebrate model of aging, *Drosophila melanogaster*.¹²⁴

An obvious question is whether disruption of mammalian IIS produces increased health span by a similar mechanism. Calorie restriction (CR) and deficiency of GH or the GHR produce robust increases in life span and resistance to stress in mice.¹²⁵ Because caloric restricted and GH-deficient/GH-resistant dwarfs have decreased levels of serum insulin and IGF-1,^{126–128} it has long been postulated that reduced IIS mediates the life-span-extending effects of CR and GH deficiency/resistance. However, recent studies suggest that GH deficiency increases stress resistance via upregulation of the Nrf2 transcription factor,¹²⁹ and that serum IGF-1 deficiency impedes expression of Nrf-2,¹³⁰ suggesting that increased protection against oxidative stress is a function of reduced GH per se. Moreover, reduced serum IGF-1 in LID mice extends median, but not maximal, life span¹³¹ and thus does not phenocopy CR or GH deficiency/resistance. Studies examining disruption of IIS signaling per se have indicated that loss of the fat cell IR increases life span,¹³² as does loss of IRS-1 in female mice,¹³³ p66 Shc,¹³⁴ and p70S6K.¹³⁵ However, the mechanisms of these effects are unclear. For example, GH-deficient/GH-resistant mice show enhanced insulin sensitivity, whereas fat cell IR knockouts and whole body p70S6K deficiency results in resistance to obesity.^{132,136} IRS-1 null mice show lifelong insulin resistance, but are protected against the development of age-related glucose intolerance presumably because of increased pancreatic insulin content, which could result in increase in insulin secretion to compensate for the insulin resistance.¹³³ GH-deficient/GH-resistant mice have an opposite metabolic phenotype: they are glucose intolerant as a result of sluggish insulin release, but are more insulin sensitive, which presumably protects them from fasting hyperglycemia.^{126,127} Thus, paradoxically, loss of GH/IIS signaling in these models may lead to certain metabolic advantages. Moreover, p66Shc may impede IIS¹³⁷; thus loss of p66Shc may enhance IIS rather than disrupting it.

Disruption of the IGF-1 receptor has yielded mixed results. In 1 study,¹³⁸ heterozygous loss of 1 IGF-1R allele extended life span by ~30% in females (significant) and ~16% in males

(insignificant). However, the overall survival of the wild-type 129 mice used in this study was 19 months, which is significantly shorter than expected in this strain.¹³⁹ When these studies were conducted on the C57Bl/6J background in conditions that resulted in robust (ie, >30 months) median survival of the wild-type control, life span was extended by only 6% in female Igf1r +/- mice and was not increased in males.¹⁴⁰ In both studies, there was evidence for resistance to oxidative stress. Because the IGF-1 heterozygous mutation protects against the development of Alzheimer disease in amouse model,¹⁴¹ it is possible that IGF-1R deficiency protects against stressors. However, the Igf1r +/- mouse develops age-related insulin resistance in females, resulting in increased sensitivity to insulin resistance and glucose intolerance induced by a high-fat diet.¹⁴² Moreover, a brain-specific knockout of the IGF-1R produced increased median, but not maximal, life span.¹²⁰ Interpretation of these results was confounded by decreased serum GH in this model. Thus, overall, it is unclear to what extent and how reduced IIS may increase mammalian health span.

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Key Points

- The GH/IGF axis is a key regulator of body size and musculoskeletal acquisition.
- The interplay between the GH/IGF axis and the insulin pathways plays key roles in carbohydrate and lipid metabolism, thus affecting the individual health-span.