Growth hormone, insulin-like growth factor 1, and insulin signaling—a pharmacological target in body wasting and cachexia

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Abstract Cachexia is an irreversible process that can develop in the course of chronic disease. It is characterized by the remodeling of the metabolic, inflammatory, and endocrine pathways. Insulin, growth hormone (GH), and insulin-like growth factor 1 (IGF-1) are involved in glucose, protein, and fat metabolism, which regulates body composition. In body wasting and cachexia, their signaling is impaired and causes anabolic/catabolic imbalance. Important mechanisms include inflammatory cytokines and neurohormonal activation. Remodeled post-receptor insulin, GH, and IGF-1 pathways constitute a potential target for pharmacological treatment in the setting of body wasting and cachexia. Peroxisome proliferator-activated receptor gamma agonists, drugs inhibiting angiotensin II action (angiotensin II antagonists and inhibitors of angiotensin-converting enzyme), and testosterone, which interfere with post-receptor pathways of insulin, GH, and IGF-1, were investigated as pharmacological intervention targets and various clinically important implications were reported. There are several other potential targets, but their treatment feasibility and applicability is yet to be established.

Keywords Angiotensin II · Cachexia · Growth hormone · Insulin-like growth factor 1 · Insulin · PPAR-γ agonist · Testosterone

Abbreviations

ATP Adenosine triphosphate
CAP Cbl-associated protein
CHF Chronic heart failure
COPD Chronic obstructive pulmonary disease
GH Growth hormone
GLUT4 Glucose transporter type 4
HOMA Homeostatic model assessment
IGF-1 Insulin-like growth factor 1
IGF1R Insulin-like growth factor 1 receptor
IRS-1/2 Insulin receptor substrate 1 and 2
JAK2 Janus kinase 2
MAFBx Muscle atrophy F-box
mTORC1 Mammalian target of rapamycin complex 1
MURF1 Muscle ring finger 1
PI3K Phosphatidylinositol 3-kinase
STAT Signal transducer and activator of transcription 5
SOCS Suppressor of cytokine signaling
1 Introduction

Cachexia is a syndrome associated with weight loss and changes in body composition due to loss of muscle mass, alterations in bone structure, and reduction of fat tissue. Over the years, various definitions have been used [1], which has caused a lack of reliable epidemiological data. After expert consensus meetings, cachexia is more precisely defined as weight loss of at least 5% in 12 months or less and fulfillment of at least three out of five criteria: decreased muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemistry [2, 3]. This definition enables the research community to perform epidemiological and intervention trials [3, 4]. In chronic disease, including chronic heart failure (CHF), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, or cancer, an ongoing inflammatory process leads to changes in metabolic and hormonal pathways. These can yield alterations in body composition and can eventually cause cachexia [4–6].

The human body regulates its composition through various hormonal effectors, including insulin, insulin-like growth factor 1 (IGF-1), and growth hormone (GH), which are primarily involved in the regulation of protein synthesis and degradation, fat mobilization, and glucose uptake and mobilization. All processes are significantly affected in cachexia. The aim of this article is to review the importance of signaling pathways in body wasting and cachexia development and to discuss some possible targets for pharmacological interventions.

2 Insulin, GH, and IGF-1 signaling

GH, IGF-1, and insulin are involved in regulating body composition through action on different body compartments. They all act as anabolic agents in skeletal muscle, promoting muscle mass gain. GH primarily regulates liver IGF-1 expression with downstream anabolic effects in skeletal muscle. In the skeleton, GH and IGF-1 induce bone growth and help maintain bone mass. Insulin and GH are involved in fat metabolism: GH induces lipolysis and insulin promotes synthesis of fatty acids in the liver and inhibits their degradation in adipose tissue [7, 8]. Generally, skeletal muscle, bone, and fat tissue are regulated by GH, IGF-1, and insulin, which can induce changes in body composition through distinct and overlapping pathways.

GH or somatotropin is a peptide produced by the pituitary gland. Its secretion is stimulated by hypothalamic GH-releasing hormone and inhibited by somatostatin, another peptide hormone secreted from the hypothalamus. There are also other stimuli that affect GH levels in serum. These include ghrelin—a peptide primarily synthesized not only in the stomach, but also in the hypothalamus and pituitary gland [9]—and other individual factors such as gender, age, diet, exercise, adiposity, and sleep. Negative feedback mechanisms of GH and IGF-1 levels are involved in regulating serum GH concentrations [10, 11]. GH binds to the growth hormone receptor (GHR), which is expressed in skeletal muscle, the liver, adipose tissue, the heart, the kidneys, and other tissues. Activation of GHR induces the synthesis of IGF-1 protein in most tissues, with the liver being the organ that contributes the major part to serum IGF-1 level. Circulating IGF-1 is bound to IGF-binding protein, which prolongs IGF-1 half-life and regulates its availability for target tissues [12, 13].

GH and other factors—for example, exercise—also induce IGF-1 expression locally in the muscle, where it acts as a paracrine modulator [14]. It has been shown that local expression of IGF-1 in CHF can be significantly reduced despite normal serum levels of IGF-1 [15]. GH binds to the insulin-like growth factor 1 receptor (IGF1R) and insulin receptor, but the affinity for the latter receptor is 100-fold to 1,000-fold lower than insulin affinity. It has to be considered, however, that IGF-1 concentrations in plasma are still 100-fold higher than those of insulin [16]. This ratio may change in the postprandial phase because levels of insulin increase in response to food ingestion, whereas food intake increases IGF-1 levels to a lesser degree [17].

Insulin receptors mainly modify glucose metabolism and can be found in the liver, adipose tissue, and muscle. However, tissues like the brain, the heart, the kidneys, and blood cells also express insulin receptors. Because of the amino acid sequence homology of the insulin receptor and IGF1R, the insulin and IGF-1 half-receptors can heterodimerize, forming an insulin/IGF-1 hybrid receptor that has higher affinity for IGF-1 and, therefore, acts more like IGF-1 than an insulin receptor [18, 19].

GH, IGF-1, and insulin exert their actions on various tissues. Signaling pathways are not the same in all organs and exact mechanisms in different cell types have not been revealed yet. The effects of GH, IGF-1, and insulin on muscle tissue have already received much attention in sports. As naturally occurring substances with anabolic and performance-enhancing effects, they have considerable potential to overcome routine doping-detection procedures and have been misused by elite athletes. Nonetheless, the research community has gained some insight into the effects of supraphysiological levels of GH, IGF-1, and insulin on muscle tissue and into other desirable and undesirable actions [20, 21]. The muscle seems to be the most important tissue affected in body wasting and cachexia processes, and loss of muscle tissue may be the most undesirable way of wasting. Therefore, this discussion focuses on signaling mechanisms of GH, IGF-1, and insulin in skeletal muscle cells.
3 Skeletal muscle

3.1 Insulin signaling in skeletal muscle

The insulin receptor consists of two α-subunits and two β-subunits, linked together with disulfide bonds. Binding of insulin to the α-subunit induces a conformational change that enables adenosine triphosphate (ATP) binding to the intracellular domain of the β-subunit. Following ATP binding, the receptor autophosphorylates, activating its protein kinase function. The insulin receptor can phosphorylate various substrates, and one of the main signaling pathways starts with the phosphorylation of insulin receptor substrate (IRS) proteins. There are six different IRS proteins (IRS-1 to IRS-6) [22], among which IRS-1 plays the main role in skeletal muscle [23]. Phosphatidylinositol 3-kinase (PI3K) recognizes phosphorylated IRS with the p85 regulatory subunit and further catalyzes phosphorylation of serine/threonine kinases with the p110 subunit (Fig. 1). The main downstream effector of this pathway is Akt kinase, which, when phosphorylated, translocates to the nucleus. There it regulates lipid, protein, and glycogen synthesis and cell survival [16].

Another important action of insulin is insulin-dependent glucose transport facilitated through glucose transporter type 4 (GLUT4) translocation to the membrane; this process can be stimulated by insulin or by other stimulatory factors like muscle contraction [24, 25]. Insulin induces GLUT4 translocation through the PI3K-dependent pathway and through the PI3K-independent pathway associated with Cbl-associated protein (CAP)/Cbl complex (Fig. 2). Herein, its role in GLUT4 transport remains questionable, especially in skeletal muscle [26, 27].

3.2 IGF-1 signaling in muscle

IGF-1 mainly acts through binding to IGF1R. This receptor is a transmembrane tyrosine kinase that autophosphorylates after IGF-1 binding. Phosphorylation creates a docking site for its substrates: IRS-1 and Shc protein. Again, IRS-1 can activate the p85 regulatory subunit of PI3K, resulting in the activation of the PI3K/Akt pathway, which inhibits cell apoptosis and promotes protein synthesis and cell differentiation. Alternatively, phosphorylation of Shc protein leads to the activation of a mitogen-activated protein kinase (MAPK) cascade, ending in induced cell proliferation [28].
3.3 GH signaling in muscle

As discussed earlier, GH exerts its effects through GHR, a transmembrane receptor, which undergoes dimerization after binding of GH. The phosphorylation of receptor-associated Janus kinase 2 (JAK2) leads to the formation of a docking site for members of the signal transducers and activators of transcription (STAT) family of transcription factors [29]. Phosphorylation of STAT5 leads to its dissociation from the receptor and translocation into the nucleus, where it regulates the expression of various genes that enable physiological actions of GH [30]. Among these genes, the expression of suppressors of cytokine signaling (SOCSs) is induced. This family of proteins negatively modulates cytokine-mediated signal transduction pathways. SOCSs, in turn, inhibit GH signaling through a negative feedback mechanism [29]. The JAK/STAT signaling pathway is also responsible for the induction of IGF-1 mRNA expression [31], although Jørgensen et al. found this to be regulated like this only in fat tissue and not in muscle [32].

There are two additional pathways in GH signaling that are triggered by JAK2 phosphorylation. First, there is the MAPK pathway, similar as in IGF-1 signaling, and second, the PI3K/Akt pathway, starting with phosphorylation of IRS proteins by JAK2 [33].

The exact mechanisms of GH signaling remain to be investigated, especially the distinction of signaling pathways in adipose tissue and muscle. Although the JAK2/STAT5 pathway seems to be fully activated with GH administration, the MAPK and PI3K/Akt pathway response to GH is questionable [29, 32].

4 The role of insulin, GH, and IGF-1 in cachexia

4.1 Insulin and GH resistance

In patients with chronic diseases such as CHF and cancer, increased levels of GH accompanied by comparatively low serum concentrations of IGF-1 have been observed. If GH is the main stimulus for IGF-1 secretion, this condition points to unresponsive peripheral tissues and GH resistance [34]. Similarly, insulin signaling becomes impaired in chronic disease and insulin resistance develops. Indeed, in patients with CHF, insulin resistance and higher insulin levels have been observed [35]. With these changes in metabolic signaling, two important anabolic stimuli that induce protein synthesis and inhibit protein degradation in muscle cells are lost. Although GH and insulin seem to have synergistic actions in promoting protein synthesis, GH actually induces insulin resistance. The exact mechanism is not known, nor is the distinction between influences of GH on insulin signaling in the liver, adipose tissue, and muscle. Increased SOCS3 expression and uncoupling of PI3K and its downstream effectors are some of mechanisms that have been suggested [29, 36].

4.2 Loss of lean mass

Loss of lean mass is a result of either increased protein degradation or decreased protein synthesis. Protein degradation/synthesis homeostasis is maintained through various mediators, including insulin, GH, and IGF-1. In human cells, protein degradation follows various proteolytic pathways, where the main five are the ATP-dependent ubiquitin–proteasome system, the calcium-dependent (calpains) pathway, the caspase system, matrix proteinases, and the lysosomal (cathepsins) pathway [5]. The ubiquitin–proteasome system seems to be importantly involved in cachectic muscle wasting because its overexpression and overactivation have been shown in various diseases related to cachexia [37, 38]. More specifically, this system is responsible for increased myosin degradation [39]. The ubiquitin protein ligases muscle atrophy F-box (MAFbx) and muscle ring finger protein 1 (MuRF1) are responsible for linking ubiquitin to proteins and targeting them for degradation in this proteasome system [38]. These ligases are regulated by the Akt/PI3K pathway, which lies downstream of IGF-1 and the insulin receptor. Moreover, it has been shown that IGF-1 and insulin also directly suppress the expression of MAFbx [40]. Protein synthesis is also regulated by the Akt/PI3K pathway because Akt forms a complex with mTORC1, a serine/threonine protein kinase that induces protein synthesis.
4.3 Inflammatory processes

Body wasting and cachexia are associated with (over)activation of the inflammatory system [5, 41, 42]. The exact interference mechanisms with metabolic and endocrine pathways are multifactorial but they remain poorly understood. Inflammatory cytokines are able to regulate cellular responses and are, therefore, also involved in the modulation of GH, IGF-1, and insulin signaling.

4.3.1 Tumor necrosis factor alpha

Tumor necrosis factor alpha (TNF-α) seems to be an important link between various forms of cachexia [5]. Indeed, its inhibitory action on heart and muscle protein synthesis has been shown [43]. TNF-α contributes to GH resistance by downregulating the expression of GHR [44]. Similarly, a connection between TNF-α and reduced expression of GLUT4, leading to insulin resistance, has been proved [45]. TNF-α also reduces phosphorylation of IRS-1 and IRS-2 by IGF1R, thus inhibiting signaling of IGF-1 in muscle cell development [46]. Moreover, it inhibits IGF-1 expression locally in muscle. Activation of transcription factor nuclear factor-κB and increased expression of MAFbx ubiquitin ligase are another two TNF-α actions; these result in the induction of protein breakdown and inhibition of myogen differentiation [47, 48].

4.3.2 Interleukin-1

Interleukin (IL)-1 is another cytokine involved in catabolic processes [49]. In hepatocytes, IL-1β and TNF-α inhibit GH-stimulated IGF-1 gene expression. On the other hand, IL-1β and TNF-α had no influence on basal IGF-1 expression [50]. IL-1β also prevents IGF-1 from promoting protein synthesis [46].

4.3.3 Interleukin-6

Interleukin (IL)-6 is a cytokine recognized to play an important role in cachexia [51]. It is produced in most cell types; the major contributor being skeletal muscle, where it is formed in response to exercise [41]. Investigating IL-6 interference with GH, IGF-1, and insulin signaling has led to various conclusions. The effects of IL-6 on insulin sensitivity in skeletal muscle show different patterns over time. They are thought to be positive in the short-term and negative after chronic exposure [52]. IL-6 not only stimulates basal IGF-1 gene expression [53], but also the expression of SOCS3, which induces ubiquitin–proteasome system-mediated degradation of IRS-1 and thereby impairs insulin/IGF1 signaling [54]. This dual role of IL-6 may not be surprising because cytokines are generally involved in regulating various pathways.

5 GH/IGF-1/insulin signaling: potential targets for cachexia treatment

An ideal drug for treating cachexia would have anabolic, anti-inflammatory, and appetite-stimulating actions. Unfortunately, an effective remedy for this devastating condition has not been found yet. GH, IGF-1, and insulin signaling pathways have already been identified as important contributors and we believe that these pathways could be clinically relevant targets for pharmacological treatment.

5.1 GH/IGF-1/insulin administration

The application of GH, insulin, and IGF-1 has already been misused by star athletes, exploiting their anabolic actions [21, 55]. To achieve an anabolic effect in cachectic patients, use of high doses of GH would be required because GH resistance is a common condition in this population [34]. Safety concerns arise when using GH for cachexia treatment because increased mortality has been associated with GH administration in critically ill patients [56]. Insulin treatment is similarly limited through insulin resistance, which is often present in cachectic patients [5]. To avoid these issues, targeting post-receptor pathways could be effective. Insulin, GH, and IGF-1 have their own receptors and signaling through specific pathways, but most of them use similar effector molecules. All three receptors (GHR, IGF1R, and IR) are tyrosine kinases, sharing the PI3K/Akt and MAPK pathway, which could be considered a pharmacological target.

However, one must bear in mind the oncogenic potential of interference with pathways promoting cell growth. Abnormalities in PI3K/Akt signaling are common in cancers and this has been widely exploited for targeted cancer treatment [57]. This raises the need for more targeted intervention, which might be offered by pharmacological entities, as subsequently discussed in this article.

5.2 Peroxisome proliferator-activated receptor gamma agonists

Peroxisome proliferator-activated receptor gamma (PPAR-γ) agonists are involved in insulin signaling (Fig. 2). Their primary action is binding to PPAR-γ receptors and stimulating transcription of genes, leading to improvement of insulin sensitivity. One potential target of PPAR-γ agonists is GLUT4. Reduced GLUT4 in skeletal muscle was shown to contribute to insulin resistance in CHF [58] and rosiglitazone was shown to induce GLUT4 translocation to the membrane in mouse skeletal muscle [59]. Rosiglitaz-
tazone also stimulates the transcription of the CAP gene [60] and pioglitazone has been shown to stimulate the expression of IRS proteins in adipocytes [61]. It is, therefore, likely that glitazones interfere with IGF-1 and GH actions. Because they act on the post-receptor pathways of these receptors, they are putative agents for treating diseases with insulin and GH resistance. Indeed, glitazones are effective in reducing GH-induced liver and skeletal muscle insulin resistance [62].

PPAR-γ agonists also affect the inflammatory component of chronic diseases, which is closely connected to the metabolic pathways shown previously. Rosiglitazone reduced plasma concentrations of C-reactive protein, IL-6, and sTNFα-R2 (a cleavage product of the activated tumor necrosis factor TNF-α receptor) in nondiabetic patients with metabolic syndrome [63]. Pioglitazone prevents THF-α-induced insulin resistance by restoring TNF-α-reduced insulin-stimulated 2-deoxyglucose uptake, tyrosine phosphorylation, and protein levels of insulin receptor and IRS-1. It also restores association of p85 with IRS-1 and PI3K activity [61]. Anti-inflammatory actions of PPAR-γ agonists are generally recognized and could be used in treating cardiovascular diseases [64]. Unfortunately, PPAR-γ agonists can lead to fluid retention, and overexpression of PPAR-γ receptors has been related to cardiac dysfunction in mice [65]. Accordingly, PPAR-γ agonists are contraindicated or require careful monitoring in patients with heart failure [66].

PPAR-γ agonists have been extensively studied in the light of their insulin-sensitizing actions, but so far, the effects of PPAR-γ agonists on muscle mass in patients with cachexia have not been investigated. There were some studies performed in patients with CHF, but the weight gain in these patients remained mostly undefined with respect to fluid retention [67].

5.3 Angiotensin II antagonists

The role of angiotensin II in vasoconstriction has been recognized and extensively investigated in arterial hypertension, whereas its role in metabolic processes and involvement in muscle wasting has been increasingly recognized in recent years. Angiotensin II has been shown to cause insulin resistance in skeletal muscle by inhibiting insulin-stimulated GLUT4 translocation, and various mechanisms have been proposed [68, 69]. Its role in muscle wasting has also been confirmed: angiotensin II was shown to promote protein degradation by lowering IGF-1 in skeletal muscle [70] and through induction of the ubiquitin–proteasome pathway [71].

There are two main pharmacologic approaches to target the effects of angiotensin II: inhibiting the formation of angiotensin II (angiotensin convertase inhibitors, ACEI) and blocking the receptor of angiotensin II (angiotensin II receptor antagonists). Because alternative ACE-independent pathways of angiotensin II formation exist, the use of angiotensin II R antagonists (“sartans”) could be more specific in targeting angiotensin II-mediated muscle wasting.

The impact of inhibitors of angiotensin-converting enzyme (ACEI) and angiotensin II R antagonists on muscle wasting in chronic diseases has already been observed because these drugs are widely used in clinical practice. Enalapril was shown to reduce the risk of weight loss in CHF patients [72] and ACEI helped maintain weight but not muscle strength in patients with congestive heart failure [73].

### Table 1 Observed effects of selected drugs on muscle function and weight in humans with CHF, COPD, or cancer

| Drug | CHF                                                                 | COPD                                                                 | Cancer                                                                 |
|------|----------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|
| PPAR-γ agonists | ↑ body weight [67]  
Maintenance of weight, but no muscle strength [73]  
↓ risk of weight loss [72, 87]  
ACEI/digoxin/diuretic combination increases muscle bulk and subcutaneous fat [88] | No data available  
No changes in body weight and no effect on exercise parameters [89] | No data available  
No data available |
| Ang II R antagonists and ACEI | ↑ functional capacity and muscle strength in elderly women [90]  
↑ functional capacity, improved symptoms; no changes in skeletal muscle bulk and hand-grip strength [91]  
Improved exercise capacity and muscle strength [86]  
No effect on skeletal muscle bulk or strength, improved exercise capacity [92] | ↑ LBM and muscle strength [93]  
Less severe weight loss [95] | ↑ body weight, ↑ fat-free mass [94]  
↑ hand-grip strength [96]  
Restored weight (primarily LBM) after weight loss [83]  
↑ body weight (but inferior to dexamethasone and MA) [97] |
| Testosterone and other anabolic steroids | | | |

CHF chronic heart failure, COPD chronic obstructive pulmonary disease, PPAR-γ peroxisome proliferator-activated receptor gamma, Ang II R angiotensin II receptor, ACEI angiotensin-converting enzyme inhibitor, LBM lean body mass, MA megestrol acetate
or hypertension [73]. Elderly patients without heart failure on antihypertensive treatment with ACEI were associated with larger muscle mass than patients receiving other hypertensive therapy [74]. In addition, insulin sensitivity was improved by losartan and lisinopril in hypertensive patients [75]. On the contrary, the TRAIN study reported no significant modifications in muscle strength after 6 months of fosinopril therapy in older persons with high cardiovascular risk profile [76].

Due to the proven clinical indications of ACEI and angiotensin II R antagonists, these studies were performed only in patients with CHF or hypertension. Moreover, the lack of cachexia definition left the patients from these studies unclassified regarding their cachectic state. Further studies are, therefore, needed to describe the role of ACEI and angiotensin II R antagonists in cachexia.

5.4 Testosterone

Testosterone, a naturally occurring anabolic hormone, has already been recognized as a substance with the potential to prevent muscle wasting and cachexia [5]. Moreover, its involvement in insulin, GH, and IGF-1 signaling has been recognized and investigated.

The influence of testosterone on insulin signaling is exerted by affecting GLUT4 and IRS-1 expression and Akt phosphorylation. This effect is dose-dependent: low doses of testosterone improve insulin sensitivity (especially in testosterone deficiency conditions) and high doses cause insulin resistance [77, 78].

IGF-1 is also associated with testosterone signaling, but the mechanism is still not clarified. IGF-1 signaling in skeletal muscle is not obligatory to mediate the anabolic effects of testosterone [79], and thus, testosterone induction of IGF-1 expression in the androgenic anabolism process is likely, but remains unproven [80, 81].

Relatively low serum levels of both testosterone and GH have been observed in elderly men. It is not surprising that application of both substances alone or in combination improved muscle protein synthesis in this population. However, a disruption in GH and testosterone signaling was suggested in elderly men [82]. It is, therefore, possible that, in cachexia, similar changes in post-receptor processes hinder the signaling of both hormones, leading to decreased production of IGF-1 in skeletal muscle along with loss of other signals important for muscle protein synthesis.

Use of testosterone or other anabolic steroids to treat muscle wasting in cachexia has been tested in different populations. In COPD patients, muscle wasting was reversed by oxandrolone, an anabolic steroid, and muscle mass and strength were increased by testosterone [83, 84]. The latter two parameters were also improved in CHF patients that received testosterone replacement [85, 86].

5.5 Evidence from clinical studies in humans

CHF, COPD, and cancer are the main conditions driving the incidence of body wasting and cachexia [4]. To cope with the increasing burden, it is plausible to focus clinical trial efforts on these conditions. Only a few trials have been completed, and most of them have demonstrated skeletal muscle/body size benefits (Table 1). Whether this translates into better outcomes remains to be established.

6 Clinical implications and future research

In cachexia, insulin, GH, and IGF-1 signaling is impaired. Although the action of these three signaling molecules on muscle tissue is essential for preserving muscle mass and function, targeting their signaling pathways should be considered in the search for new compounds for cachexia treatment. Due to the lack of response to the basic stimuli of insulin, IGF-1, and GH in muscle cells in cachexia, two approaches seem reasonable: (1) targeting post-receptor pathways—for example, with PPAR-γ agonists, or (2) using alternative pathways in muscle cells to reach the same targets inside the cell (angiotensin II R antagonists/ACEI and testosterone). Several studies have addressed this issue, but the results do not fully support implementation in clinical practice. Potential pharmacological targets can be found among the effector molecules involved in overlapping pathways of GH, IGF-1, and insulin signaling.

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