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The therapeutic potential of IGF-I in skeletal muscle repair

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Abstract

Skeletal muscle loss due to aging, motor neuron degeneration, cancer, heart failure and ischemia is a serious condition for which currently there is no effective treatment. Insulin-like growth factor 1 (IGF-I) plays an important role in muscle maintenance and repair. Preclinical studies have shown that IGF-I is involved in increasing muscle mass and strength, reducing degeneration, inhibiting the prolonged and excessive inflammatory process due to toxin injury and increasing the proliferation potential of satellite cells. However, clinical trials have not been successful due to ineffective delivery method. Choosing the appropriate isoforms or peptides and developing targeted delivery techniques can resolve this issue. Here we discuss the latest development in the field with special emphasis on novel therapeutic approaches.

Keywords

muscle wasting; IGF-I; satellite cell

IGF-I and IGF-II in skeletal muscle maintenance

IGF-I is a circulating hormone originating from the liver and responsive to growth hormone (GH) stimulation[1]. It is also synthesized in skeletal muscle and regulates muscle growth in an autocrine/paracrine fashion[2]. IGF-I has been considered as a biomarker of health and fitness; indeed, higher circulating IGF-I concentrations are positively associated with a number of health parameters related to body composition and cardiovascular health, and negatively associated with body fat [3]. IGF-I is also positively associated with measures of aerobic fitness and muscular endurance [3]. Pathological conditions such as malnutrition, critical illness, sepsis, high doses of exogenous glucocorticoids and inflammation are associated with lower IGF-I mRNA in muscle[2]. IGF-I signaling is mediated via its binding to the IGF-I receptor (IGF-IR), a transmembrane protein with tyrosine kinase activity[2] and

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activator of the PI3K/Akt pathway [4]. Its action is also regulated by binding to at least 6 small carrier proteins called IGF-I binding proteins, that bind to IGF-I in extracellular fluid and the circulation (Box 1). However, the role of IGF-I in the area of load induced muscle hypertrophy has been recently questioned. Mechanical loading can activate mTOR Complex 1 (mTORC1) signaling and promote muscle hypertrophy[5]. Also, the hypertrophic response induced by mechanical-overload is fully preserved in muscles from transgenic mice that expresses a dominant negative IGF-I receptor specifically in skeletal muscle[6]. Furthermore, IGF-dependent signaling toward enhanced protein synthesis via the Akt-mTOR-S6K pathway is not always observed after strength type exercise in humans and in rodents[7].

Similar to IGF-I, IGF-II is also important for muscle growth and differentiation. IGF-II promotes the differentiation of muscle cell lines in an autocrine fashion[8]. Transforming growth factor beta (TGF-β) blocks IGF-II gene activation in differentiating myoblasts and thereby interrupts an IGF-II-initiated autocrine amplification cascade that drives early events in muscle differentiation[9]. Furthermore, exogenous IGF-I or IGF-II can restore differentiation in the presence of TGF-β, indicating that IGF-II may be effective in treating sarcopenia in which TGF-β plays a pathogenic role[9].

IGF-I isoforms in myogenic signaling, muscle growth and development

Physiologic skeletal muscle maintenance requires proper stimulation from tension and stretch which induce the expression of IGF-I[2, 10–14]. The IGF-I gene is spliced in response to mechanical signals to produce various isoforms of IGF-I with different actions[15] (see Box 2,Fig. I). IGF-IEa is up regulated by a single ramp stretch of 1-h duration but reduced by repeated cyclical stretch[15]. In contrast, IGF-IEb is up-regulated by cycling loading[15]. When the normal tension and stretch are not in place, the IGF-I signaling pathway becomes inactivated and leads to muscle atrophy, as shown in astronauts working in microgravity environments[16]. The effect of microgravity on skeletal muscles has been examined in C57BL/10J mice through the mice drawer system (MDS) program[16]. In this experimental setting, atrophy was evident in soleus muscle, but was absent in extensor digitorum longus (EDL) muscle, following 91 days of long-term exposure to real microgravity in space. Expression of IGF-I was reduced in soleus muscle and increased in EDL muscle, suggesting that IGF-I signaling pathways may be impaired selectively in soleus muscle[16]. Reduced muscle tension also led to up-regulation of the E3 ubiquitin-protein ligase Nedd4, which only occurs in disuse atrophy but not in atrophy resulting from starvation or diabetes [17].

IGF-I actions on muscle satellite cells (SCs)

The myogenic progenitor SCs can be activated upon tissue damage and become myoblasts, which replace damaged myofibers via differentiation and fusion[18]. Muscle damage induces the expression of the IGF-I isoform mechano growth factor (known as MGF, see glossary) followed by that of the calcium-dependent cell adhesion molecule and marker of satellite cells M-cadherin. However, as expression of IGF-IEa peaks later than M-cadherin[19], MGF may be the initial IGF-I isoform that triggers the activation of SCs, followed by the later expression of IGF-IEa to maintain protein synthesis[19]. Recent studies suggest that SCs are also involved in exercise induced muscle hypertrophy. Individuals with a greater basal presence of SCs have a remarkable ability to expand the SC pool, incorporate new nuclei, and achieve robust growth with training[20]. In addition to IGF-I, several other factors (see Box 3) also contribute to muscle maintenance and adaptation. Therefore, muscle repair is initiated by the release of MGF as a result of injury, followed by activation of SCs and the levels of SC reserve determine the potential for muscle regeneration.

IGF-I in animal models of muscle wasting, neuromuscular disorders and injury

Sarcopenia

Sarcopenia is caused by a multitude of factors which include chronic inflammation, blood vessel dysfunction, denervation, malnutrition, physical inactivity, and is characterized by decreased muscle strength and selective type II fast fiber atrophy. The decline in muscle tissue regeneration is due to a decreased activation of the Notch pathway[21] and an increase in TGF-β signaling[22] (Fig. 1). Indeed, aging muscles produce excess TGF-β which induces high levels of pSmad3 in satellite cells [22], thus antagonizing Notch and satellite-cell proliferation. The decreased activation of Notch is unable to block the TGF-β-dependent up-regulation of cyclin-dependent kinase (CDK) inhibitors, resulting in reduced satellite cell activation [22]. In addition, increased expression of TGFα also reduces expression of Notch ligand and receptor in aged skeletal muscle and contributes to loss of muscle mass and function with aging[30].

Despite the imbalance between Smad3 and Notch in aging muscle, there are evidence to suggest that old satellite cells retain the capacity to self renew [23], and regenerate muscles upon injury[24]. Muscle precursor cells obtained from young and elderly people have similar myogenic potential when cultured in vitro[25]. Shavlakadze et al[24] showed that there was an initial delay of new muscle formation at 5 days, followed by extensive myotube formation at 10 days, in geriatric muscle autografts, confirming excellent intrinsic capacity of old myogenic stem cells to proliferate in vivo. The initial delay of muscle formation was due to a reduced inflammatory response of old hosts[24]. Furthermore, it has been shown that proliferating satellite cells may not be able to fuse with denervated muscle fibers[26]. These studies suggest that the muscle regeneration is a complicated process which is dependent on not only the myogenic capacity of satellite cells but also on the microenvironment of the host.

Blood flow decreases with aging due to increased sympathetic vasoconstriction, arterial stiffening and narrowing[27]. Low numbers and impaired function of endothelial progenitor cells (EPC)[28] is also observed, an independent risk factor for atherosclerosis which causes narrowing of blood vessels and muscle weakness in elderly subjects. Along these lines, treatment of aged mice with IGF-I increased EPC levels and improved EPC function[28].

Interleukin-6 (IL-6) and tumor necrosis factor alpha (TNFα) are found elevated with aging. Both cytokines induce muscle atrophy via either direct catabolic effects or through indirect mechanisms such as inhibition of IGF-I production and its signaling pathway[29]. The denervation seen in sarcopenia may be related to elevated oxidative stress, decreased presence of ciliary neurotrophic factor (CNTF), a potent survival factor for neurons, and vascular endothelial growth factor (VEGF)[30].

Aging affects the nervous system at multiple levels, including the motor cortex , the spinal cord, peripheral neurons, and the neuromuscular junction[31]. Targeted delivery of IGF-I to spinal cord motor neurons via intramuscular injection of IGF-I, fused to non-toxic tetanus toxin fragment-C (TTC), promoted maintenance of muscle fiber innervation and prevented neuromuscular junction atrophy and fragmentation in aged muscle fibers[32].

An age-related deficit in IGF-I receptor activation has been demonstrated in the muscle of old rats[33]. It has been shown that resistance exercise induces phosphorylation of the IGF-I receptor, and an increase in Akt in young but not old muscles[33]. Thus the impairment of IGF-I receptor signaling might negatively affect the delivery of IGF-I, even though animal studies have shown that IGF-I is useful in treating sarcopenia. One way to solve this

problem is to activate the PI3K/Akt-mTOR pathway, downstream of the IGF-I pathway, by other means. Burks et al[34] has shown that losartan, an inhibitor of the angiotensin II type 1 receptor (AT1), was able to combat disuse atrophy in aged mice that were subjected to hindlimb immobilization, and this protective mechanism was due to an increased activation of the Akt/mTOR pathway. Along this line, angiotensin converting enzyme inhibitors (ACEIs) positively modulate the IGF-I system and ACEIs users exhibit significantly higher muscle strength[35]. Testosterone is another important player in muscle adaptation to excercise. Several studies have reported that the administration of testosterone improves lean body mass and maximal voluntary strength in older men[36]. Therefore, Losartan, ACEIs, testosterone are potential candidates that could be used in conjunction with IGF-I to counteract sarcopenia.

Neuromuscular diseases

Amyotrophic lateral sclerosis (ALS)—ALS is a degenerative disease caused by gain of function mutations associated with a dominant SOD1 phenotype, a gene encoding the cytosolic antioxidant enzyme Cu, Zn-superoxide dismutase. Interestingly, ALS symptoms can be counteracted by localized expression of IGF-I in the skeletal muscle of an SOD1 transgenic mouse model[37]. In this context, a clinically relevant approach would be to deliver IGF-I systemically. Indeed, Saenger et al[38] investigated the effect of systemic administration of polyethylene glycol (PEG) modified IGF-I (PEG-IGF-I) in two SOD1-G93A mouse lines, the G1L with a milder and the G1H with a more severe phenotype. PEG-IGF-I was generated by site-specific addition of PEG to lysine 68.

Results showed that in G1L mice, but not in the G1H mice, PEG-IGF-I treatment significantly improved muscle force, motor coordination and animal survival [38]. Therefore, additional interventions are needed to cure the severe form of ALS. In this context, Van Hoecke et al screened a zebrafish model of ALS and identified Epha4, a receptor in the ephrin axonal repellent system, as a modifier of the disease phenotype in fish, rodents and humans[39]. Genetic as well as pharmacological inhibition of Epha4 signaling was able to rescue the mutant SOD1 phenotype in zebra fish and increased survival in mouse and rat models of ALS by promoting neuromuscular re-innervation in late stages of ALS[39].

Spinal and bulbar muscular atrophy (SBMA)—The neurodegenerative disease SBMA is caused by expansion of a CAG repeat encoding polyglutamine in the androgen receptor (AR) gene, resulting in accumulation of AR and loss of motor neurons in the brainstem and spinal cord. Augmentation of IGF-I levels in the muscle increases AR clearance through the ubiquitin-proteasome system and AR phosphorylation by Akt[40], and in a mouse model of SBMA, muscle-specific overexpression of IGF-I was able to improve motor performance and body weight [40]. Collectively, these data suggest that IGF-I has a direct inhibitory effect on mutant AR, which might help prevent motor neuron degeneration in SBMA.

Spinal muscular atrophy (SMA)—Survival motor neuron protein (SMN1) is a protein often found mutated in SMA. Mice with severe SMA have abnormal motor function, retarded muscle growth and reduced circulating IGF-I level [41]. The SMAΔ7 mice that overexpress a muscle specific IGF-I isoform (mIGF-I) display enlarged myofibers and increased median survival, compared with mIGF-I-negative SMA littermates[42]. However, this was not associated with a significant improvement in motor behavior[42], suggesting that targeting muscle alone without restoring motor neuron function is not sufficient to reverse a severe form of SMA. However, in the $Smn^{+/-}$ mice which is a mouse model of mild forms of SMA, muscle strength was maintained because the loss of motor neurons was

compensated by sprouting from remaining motor axon terminals[43]. The mechanisms involved in motor axon sprouting are complex. It may be controlled by nerve growth factors, cytokines and neurotrophic factors like CNTF. These factors are released from the Schwann cells, then transferred into the perineurium by diffusion[43] (Fig. 2). Indeed, CNTF was shown to prevent disease associated denervation and axon pruning in the ALS SOD1-G93A mouse line discussed above [44].

Duchenne Muscular Dystrophy (DMD)—DMD is one of the most prevalent types of muscular dystrophy affecting mainly males, characterized by rapid progression of muscle degeneration that occurs early in life. The disorder is caused by the lack of dystrophin, a skeletal muscle cell protein required for structural support. Several recent studies have shown very promising results with IGF-I treatment for DMD[45, 46]. Secco et al., showed that systemic delivery of human mesenchymal stromal cells combined with IGF-I enhances muscle functional recovery in LAMA2dy/2j, a mouse model for duchenne muscular dystrophy [47]. Using the dystrophic mdx mouse model, Gordon Lynch's group showed that administration of LR IGF-I, which is an analogue of IGF-I with significantly reduced binding affinity for IGFBPs, improved the dystrophic pathology by reducing the susceptibility to muscle injury[48]. Interestingly, the protection conferred by LR IGF-I was independent of changes in muscle fatigue and oxidative metabolism[48]. Mecasermin rinfabate, a complex of equimolar amounts of IGF-I and IGFBP-3, has been approved by the U.S. Food and Drug Administration for treatment of severe primary IGF deficiency and currently efforts are being made to explore its use in various muscle wasting conditions[49]. It has been shown recently that twice-weekly PEG-IGF-I subcutaneous injections for 6 weeks protected the diaphragm muscle against fatigue, and the tibialis anterior muscle against contraction-induced injury in young mdx mice[50].

The ability of IGF-I to prevent muscle deterioration has been shown in a variety of muscle wasting models. However, in the clinical situation, when patients are presented to their physicians, muscle wasting conditions have already existed for a while. Thus, the question is whether IGF-I would be useful to reversing established wasting conditions. In this regard, Lynch et al[51] has shown that systemic IGF-I treatment improved the functional properties of skeletal muscles from 129P1 ReJ-Lama2^{dy} dystrophic mice, a mouse model for congenital muscular dystrophy. These mice are characterized by progressive weakness and paralysis beginning at about 3 1/2 weeks of age. IGF-I was administered to the mice later than 4 weeks of age, when the animals have already developed muscular dystrophy, However, after 4 weeks of IGF-I treatment, the muscle dystrophy were reversed. Similarly, in a recent study by Secco et al., systemic delivery of human mesenchymal stromal cells combined with IGF-I, enhanced muscle functional recovery, in LAMA2dy/2j dystrophic mice[47]. Similarly, in 18 months old mice with sarcopenia, a reversal of the deleterious effects of aging on muscle structure and function by intramuscular injection of IGF-I fusion protein[32], was also observed.

Diabetic neuropathy—Diabetes associated sensory and motor neuron damage is characterized by decreased circulating levels of IGF-I[52]. Chu et al showed that systemic levels of IGF-I can be restored by intravenous delivery of an AAV vector encoding mouse IGF-I(Eb) cDNA, in a streptozotocin (STZ)-induced mouse model of diabetic peripheral neuropathy. This treatment reversed neuronal deficits, improved motor function, and prevented the STZ-induced loss of skeletal muscle[52]. Overall, animal studies have shown beneficial effects of IGF-I in the treatment of various neuromuscular disorders, although the effects were more evident in the mild forms of the diseases.

Cancer cachexia

Cancer cachexia is a syndrome characterized by progressive loss of muscle and fat, anorexia, and metabolic abnormalities[53], driven by varied underlying mechanisms. In the murine MAC16 colon tumor model of cachexia [54], angiotensin II plays a major role by inducing direct catabolism in isolated myotubes, which can be inhibited by IGF-I[54, 55]. Other studies[56] have shown that activation of the myostatin/Activin A receptor ActRIIB is responsible for loss of muscle in the colon 26 (C26), the melanoma G361 and the ovarian carcinoma TOV21G cancer cachexia models. ActRIIB inhibition prevents muscle wasting and prolongs survival[56] via increased Akt activity, inactivation of FOXO3a and subsequent inhibition of Atrogin-1 and MuRF1[56]. Akt is a critical kinase downstream of IGF-I action and most of IGF-I's anabolic and anti-apoptotic effects are mediated by phosphorylation and activation of Akt. In this model, myostatin induced down regulation of Akt, p70S6 kinase and FoxO1 phosphorylation can be restored by treatment with IGF-I, suggesting that IGF-I/Akt signaling is dominant over inhibition of the myostatin/Smad/Akt pathway [57]. In the Yoshida hepatoma rat model[58], low-dose of IGF-I, delivered subcutaneously, reduced mortality and attenuated loss of body weight as well as muscle mass. However, a recent study questioned the role of IGF-I in cancer cachexia in the C26 tumor model; in the skeletal muscle of tumor hosts, the levels of phosphorylated Akt were comparable to controls, or even increased, and loss of muscle mass or reduction of fiber size in these mice were not modified by IGF-I gene transfer in the tibialis muscle, while IGF-I gene transfer prevented skeletal muscle atrophy in senescent mice[59]. These studies suggest that IGF-I may be a potential drug target for the treatment of cachexia associated with certain, but not all types of cancers.

Heart failure cachexia

Chronic heart failure is characterized by compromised ventricular systolic or diastolic function or both. The disease results in reduced exercise tolerance, stimulation of the sympathetic nervous system, and the resilience of neurohormonal activation[60]. Specific neurohormones that are frequently involved include noradrenalin, atrial natriuretic peptide, several hormones in the renin–angiotensin–aldosterone system (RAS), reactive oxygen species (ROS) and activation of the ubiquitin-proteasome pathway[12]. Progression of disease increases RAS activation resulting in an upregulation of angiotensin II. In turn, angiotensin II downregulates both circulating and skeletal muscle IGF-I[61]. Importantly, IGF-I and its binding proteins exert acute anabolic effects on metabolism as well as mediating myoblast proliferation, differentiation, and apoptosis[2].

IGF-I also is known to play a role in compensatory hypertrophy. Intriguingly, IGF-I levels are downregulated in heart failure models[62]. Alterations of RAS hormones and IGF-I levels, together with reduced skeletal muscle blood perfusion (a consequence of increased sympathetic nervous system activity), alter the aerobic and anaerobic enzymatic activity of skeletal musculature. Chronically, this can transform the composition of skeletal muscle fibers[63], thus giving rise to highly fatigable muscle that manifests in exercise intolerance and weakness. These functions may make IGF-I and its binding proteins good markers of skeletal muscle molecular changes and useful for understanding the peripheral effects of heart failure.

Recent studies have shown that there were significantly more myosin heavy chain (MHC) isoforms coexpressing one or more pure MHC hybrids in heart failure patients, compared with the control subjects[63]. Additionally, there was a significant difference in the MHC IIa/IIx hybrid isoforms between the two groups[63], suggesting a molecular shift in the muscle of heart failure patients to a highly fatigable fiber type that may account for classical symptoms such as exercise intolerance[63].

Results from skeletal muscle biopsies indicated that IGF-I mRNA expression was fivefold lower in patients with heart failure, compared with the control subjects. The reduction in local IGF-I expression was accompanied by a 15-fold decrease in local IGFBP-5 mRNA expression in heart failure, compared with control subjects[63]. These decreases in local IGF-I and IGFBP-5 could be an indication of the inability of heart failure skeletal muscle to undergo a compensatory hypertrophy. Additionally, reduction of these transcripts might imply that heart failure muscle is not capable of regeneration through upregulation of myoblast proliferation or differentiation[63].

The muscle quality (torque) was significantly less in the heart failure patients compared with the control subjects, meaning that for a given area of muscle, the heart failure patients produced less force. Tracy et al[64] regards this phenomenon as alterations in neuromuscular input. Whole-muscle cross-sectional area (CSA) and IGF-I mRNA expression was highly correlated in the chronic heart failure group, with no significant correlation detected in the control group. This correlation describes that 86% of the variability in whole-muscle CSA is accounted for by the variability in IGF-I mRNA expression in these heart failure patients. This would imply that molecular changes can be found prior to whole-muscle changes with heart failure and that IGF-I mRNA expression might be an early predictor of disruptions in muscle function[63].

These data indicate that decrements in IGF-I and IGFBP-5 levels in the skeletal muscles of Class II heart failure patients play critical roles in MHC isoform distribution, which switch to more glycolytic properties, evidenced by a significant increase in hybrid isoforms and in particular the MHC IIa/IIx isoforms. These negative alterations may partly be explained by the strong correlation in mRNA IGF-I expression and whole-muscle CSA and the decrease in whole-muscle quality. Future directions for research include addressing the specific single muscle fiber physiological alterations such as peak force, maximal shortening velocity, and peak power, that are occurring with heart failure in conjunction with the IGF-I system and other growth factor systems[63].

Ischemia reperfusion injury

Ischemic injury occurs when the blood supply to an area of tissue is cut off. Restoration of the blood supply leads to additional damage due to the influx of inflammatory cells and cytokine release [65]. This phenomenon has been termed ischemia reperfusion (I/R) injury. Hammers et al[65] found an age-related reduction in the expression of IGF-I and individual IGF-I Ea and Eb splice variants as well as IGF-I receptor signaling, following injury. By evaluating the controlled release of IGF-I from a biodegradable (PEG)ylated fibrin gel matrix and the subsequent recovery of skeletal muscle from I/R[66], they showed that PEG-IGF-I treatment resulted in significant improvement of muscle function and structure. The beneficial effect exerted by IGF-I on I/R injury is consistent with previous findings that IGF-I accelerates muscle regeneration by modulating inflammatory cytokines[67].

Clinical applications of IGF-I

Why IGF-I trials have failed?

Clinical applications of IGF-I have been attempted, but few have proceeded to Phase III human trials, except for ALS studies. Even for the ALS trial, the subcutaneous injection of IGF-I in ALS patients did not show beneficial effects[68]. As Howe et al[69] pointed out, this negative effect may be explained by the low bioavailability of IGF-I within the brain parenchyma. In reply to Howe's comment, Surenson et al[69] acknowledged that the effectiveness of subcutaneously administered IGF-I is still unclear and new delivery mechanisms need to be developed. In fact, many of the drug delivery strategies thus far have yielded limited success, most likely related to rapidly depleted local concentrations resulting

from bolus drug delivery. Using biodegradable polymeric systems, which provide localized and sustained growth factor release, could solve this problem. Another potential problem may be that IGF-I alone is not sufficient to accomplish all the tasks that are required to reverse muscle atrophy in all forms of motor neuron degenerative diseases. As discussed above, muscle atrophy in ALS is secondary to motor neuron degeneration caused by mutations in SOD1 and other genes. Therefore, therapeutic interventions targeting either SOD1 or Epha4, in combination with IGF-I, may offer better outcome. The findings by Saenger et al[38] that systemic delivery of IGF-I was beneficial for mice with a milder but not severe phenotype of ALS suggest that IGF-I may have some limited neuron protective effect, but not sufficient to cure the disease.

How IGF-I should be delivered and which isoform of IGF-I should be used?

Whereas IGF-I therapies for muscle wasting have been shown beneficial in animal studies, dosing issues and potential side effects remain major obstacles in clinical application.

In order to avoid the potential oncogenic effect associated with IGF-I, the therapeutic potential of the MGF-24aa-E peptide should be explored since this peptide alone has a marked ability to enhance SC activation, proliferation and fusion for muscle repair and maintenance [70].

The intranasal delivery of proteins has recently emerged as an effective method to deliver proteins to the central nervous system (CNS)[71]. A randomized, double blind, placebo-controlled trial examined the effects of intranasal insulin administration on cognition, function, cerebral glucose metabolism, and cerebrospinal fluid biomarkers in adults with amnestic mild cognitive impairment or Alzheimer disease (AD) [72]. The data from this trial suggests that the administration of intranasal insulin may have a therapeutic benefit for adults with AD [72].

Local delivery of IGF-I is an alternative approach, if systemic route cannot achieve desired concentrations. A biodegradable microsphere loaded with N-glycosylated recombinant glial cell-derived neurotrophic factor (GDNF) was injected into the rat striatum by stereotaxic surgery two weeks after a unilateral partial nigrostriatal lesion induced by the neurotoxic oxidopamin (that selectively destroys dopaminergic neurons). This demonstrated that GDNF-loaded microspheres improved the rotational behavior induced by amphetamine [73].

What other interventions are needed for muscle repair in addition to IGF-I?

Since the underlying mechanisms of muscle atrophy in various diseases are different, it is unlikely the IGF-I would be a universal miracle drug that cures all forms of wasting condition. It may be necessary to deliver multiple growth factors or drugs targeting the specific pathogenic process in order to drive muscle repair to completion (Fig. 3). For example, IGF-I has been used in combination with VEGF to treat ischemia reperfusion injury[74]. In this case, the underlying problem is ischemia and VEGF's role is to promote angiogenesis and prevent necrosis in ischemic hindlimbs[74]. IGF-I plays an important role in protecting cells from apoptosis, inducing myoblast proliferation and myogenic differentiation[74]. ACEIs have been shown to improve skeletal muscle strength by enhancing muscle blood flow, increasing glucose uptake and lessening inflammation[35]. These actions of ACEIs are complementary to IGF-I's anabolic effects. Along these lines, ACEIs improves physical function and exercise capacity in patients with congestive heart failure[75]. Furthermore, immobilized mice treated with the AT1 blocker losartan were protected against loss of muscle mass[34]. Therefore, inhibition of the renin–angiotensin system in conjunction with IGF-I may offer additional benefit for treating cardiac cachexia and other muscle wasting conditions (Fig. 3). Loss of skeletal muscle in cancer cachexia

results from activation of ActRIIB pathway [56]. Thus, it is likely that ActRIIB blockade, in combination with IGF-I may provide better therapeutic benefit for cancer associated muscle loss (Fig. 3).

Side effects of IGF-I therapy and solutions

Hypoglycemia and suppression of GH release are main acute side effects after systemic IGF-I delivery. In this regard, studies on PEG-IGF-I have shown little side effect and no loss of long-term beneficial activity. The main concern with IGF-I treatment is the risk for cancer. Gao et al[76] examined serum IGF-I, IGF-II and IGFBP-3 levels in relation to risk of advanced colorectal adenoma in a case-control study and found that IGF-I and IGF-II, but not IGFBP3 levels were associated with colorectal adenoma risk[76]. IGF-I is also associated with increased risk for prostate cancer[77]. In this context, a plausible solution is to determine the optimal dose and duration that would provide maximal benefit without causing cancer in animal models and to explore the potential therapeutic effect of the synthetic MGF peptide in clinical trials. It should be emphasized that although some evidence exists that life-long elevated IGF-I levels may confer a certain risk to cancers, this is completely different to the pure speculation that several years of chronic IGF-I therapy provides the same risk. Implementing local applications in (sub)acute muscle injury paradigms may be a way to avoid the concerns of potential cancer risk. In this context, Nystrom et al[78] examined the ability of a sustained local administration of IGF-I to prevent sepsis-induced muscle atrophy, over a 5-day period. At the time of cecal ligation and puncture or sham surgery, mice had a time-release pellet containing IGF-I implanted next to the gastrocnemius. The data showed that local delivery of IGF-I prevented sepsis-induced loss of muscle mass without having undesirable side effects on metabolic processes in distant organs. Furthermore, IGF-I delivery also inhibited the expression of IL-6 and atrogin-1 within the muscle.

Concluding remarks

Numerous animal studies demonstrate IGF-I as a powerful growth factor for muscle repair. There are, however, several important questions which remain unanswered (see Box 4). The effect of muscle specific IGF-I isoforms, the MGF C-terminal peptides and IGF-I fusion protein targeting spinal cord motor neurons should be explored in clinical trial. IGF-I may be beneficial in the mild types of motor neuron diseases since IGF-I is a pro-survival factor for motor neuron-derived cells[79]. However, for the severe forms of motor neuron diseases such as ALS and SMA, the real challenge is the underlying defect in the neuron, which has to be overcome before IGF-I could show any beneficial effect. To this end, mIGF-I for the treatment SBMA represents a significant breakthrough of targeted therapy for neuromuscular diseases. Motor neuron axon sprouting appears to be an important mechanism for reinnervation of myofibers and this process requires CNTF. Although IGF-I also has some neurotrophic effects, its main action is to promote muscle hypertrophy and activation of satellite cells via PI3K/AKT pathway. Therefore, for neuromuscular diseases, the combination of both CNTF and IGF-I may be a better solution. For more severe forms of neuromuscular diseases in which compensatory mechanisms by axon sprouting is no longer possible, stem cell based therapy would be a potential option[80].

The route of IGF-I administration is also an important factor for successful intervention. For sarcopenia or any other conditions involves dennervation, we propose local intramuscular injection of IGF-I fusion protein that targets spinal cord motor neurons. The injection of a tetanus toxin fragment-C (TTC) fusion protein in aged mice was shown to prevent age-related alterations to the nerve terminals at the neuromuscular junctions[32]. For other wasting conditions, MGF or PEG-IGF-I could be delivered by implantation of a time-release pellet[78].

Although ACEIs improves physical function in patients with heart failure[75], it is not known whether the beneficial effect of ACEIs is due to improvement of heart function or via a direct effect on skeletal muscle, therefore, muscle strength should be tested in future studies in heart failure patients treated with ACEIs. Many cytokines/soluble factors are released after muscle injury and during wasting. The identification of the master switch that triggers a particular wasting condition is the key for successful intervention. This could be accomplished by mRNA expression profiling or cytokine array analysis of differentially expressed mRNAs/cytokines in paired muscle samples. Once target genes or cytokines are identified, transgenic mice overexpressing candidate gene constructs will be useful for testing whether a gene is sufficient to induce atrophy. Finally, the expression of the gene or its related pathway should be examined in muscle biopsies from patients experiencing wasting. A good example is the discovery of Nedd4 as a unique trigger for disuse atrophy[17]. Nedd4 deserves further study using knockout approach and pharmacological inhibition of Nedd4 in conjunction with IGF-I/Akt activation should also be explored in animal models of disuse atrophy.

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Glossary

Activin A	a growth factor that stimulates synthesis and secretion of follicle stimulating hormone (FHS). Activin A was recently found to be associated with muscle loss in cancer models
Amyotrophic lateral sclerosis (ALS)	a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord
Cachexia	The loss of body weight and muscle mass that cannot be reversed by eating more food due to a catabolic mechanism
Ciliary neurotrophic factor (CNTF)	a polypeptide hormone and nerve growth factor primarily found in the nervous system where it promotes neurite outgrowth and collateral axon sprouting

Mechano growth factor (MGF), endogenous	the IGF-IEc isoform (IGF-IEb in rodent), also called MGF, is produced when skeletal muscles are subjected to stretch or exercise
Mechano growth factor (MGF), synthetic	A synthetically manufactured peptide corresponding to the 24 most C-terminal residues of IGF-IEc which has been shown to promote cellular proliferation and survival
Muscle torque	the force generated from a group of muscles, which can be pushing or pulling
MyoD	a basic helix loop helix (bHLH) transcription factor that belongs to the family of myogenic regulatory factors (MRFs). MyoD is expressed in activated satellite cells and is a marker of myogenic commitment
Myogenin	a member of the MRF family of transcription factors and a marker of myogenic differentiation. Myogenin is involved in the coordination of skeletal muscle development and repair
Myostatin	a secreted growth differentiation factor and member of the TGF-p protein family. It is a negative regulator of skeletal muscle growth
Stem cell niche	a microenvironment that plays an important role in keeping stem cells in quiescent state and which is indispensable for the maintenance of stem cells
Sarcopenia	degenerative loss of skeletal muscle mass, function, and strength associated with aging and characterized by selective type II fast fiber atrophy
Notch signaling pathway	a highly conserved cell signaling pathway important for cell-cell communication and control of multiple cell differentiation processes
Satellite cells (SCs)	Quiescent myogenic progenitor cells, which are located between the sarcolemma and basement membrane of muscle fibers
Spinal and bulbar muscular atrophy (SBMA)	a disorder characterized by degeneration of motor neurons in the brain stem and spinal cord. The condition is inherited in an X-linked recessive manner and is associated with mutations in the AR gene
Spinal muscular atrophy (SMA)	an autosomal recessive disease caused by a genetic defect in the SMN1 gene which codes for a protein necessary for survival of motor neurons

Box 1

IGF-I signaling and binding proteins

IGF-IR signaling pathways

IGF-IR consists of two α-subunits and two β-subunits. The extracellular α-subunits contain the ligand binding sites whereas the β-subunits are transmembrane domains that contain the tyrosine kinase activity. Upon IGF-I binding, the β-subunits undergo conformational change which causes activation of the internal kinase activity and autophosphorylation of the kinase domain which then phosphorylates insulin receptor substrate-1 (IRS-1)[81]. Once phosphorylated on tyrosine residues, IRS-1 acts as a docking protein for several effector molecules possessing Src homology 2 domains, including p85, the regulatory subunit of PI-3 kinase (PI-3K). PI-3K activation leads to phosphorylation of Akt which then transmit signal to mammalian target of rapamycin (mTOR) and p70S6 kinase. Activation of this pathway results in protein synthesis, hypertrophy and inhibition of the key ubiquitin ligase *atrogin-1* by inactivating Foxo factors[82], IGF-IR also phosphorylates Shc, which subsequently activates the RAS/Raf/MEK pathway leading to cell proliferation and mitogenesis[2].

IGF binding proteins

IGF binding proteins (IGFBPs) are small carrier proteins that bind to IGF-I or IGF-II in extracellular fluid and in the circulation. IGFBPs have higher affinity for IGF than IGF-IR, acting as a depot for slow release of IGF. Six different types of IGFBPs have been found so far. The mRNA levels of all 6 types of IGFBPs can be detected in regenerating muscles but at different time points[83]. For example, the expression of IGFBP-2 and IGFBP-3 mRNAs in regenerating muscles increases at 12 h and correlates with those of proliferating cell nuclear antigen (PCNA) and MyoD, markers for proliferating cells and activated satellite cells, respectively[83]. In contrast, the expression of IGFBP-1 and IGFBP-5 mRNAs starts to increase 72 h after muscle damage and is similar to those of p21 and myogenin mRNAs which are mainly involved in myogenic differentiation[83]. IGFBP1–4 proteins are present in the immature muscle fiber nuclei and the extracellular matrix in regenerating muscles[83], suggesting that these proteins may have independent functions as transcription regulators. Overexpression of IGFBP-2 significantly inhibits postnatal skeletal myofiber growth by decreasing myogenic proliferation and protein accretion and enhances glycolytic muscle metabolism[84]. Mice overexpressing IGFBP-5 have low birth weight[85].

Box 2

IGF-I isoforms

The IGF-I polypeptide contains 70 amino acids. The IGF-I gene has two promoters and six exons and transcribes at least six different mRNAs due to alternative splicing. Exon 1 or 2 encodes the initial amino acids of a leader peptide. Exon 3 encodes the remaining of the leader peptide and a portion of the mature IGF-I peptide. Exon 4 encodes the remaining part of the mature peptide and the first 16 amino acids of the E peptides. The rest of the E peptide is encoded by exon 5 (Eb), exon 6 (Ea) or an insert from exon 5 (49 bp in humans, 52 bp in rodents) spliced onto exon 6 (Ec). This insert from exon 5 causes a frameshift such that the sequence of the Ec is not the same as other E peptides[86]. Therefore, IGF-IEa, IGF-Eb and IGF-Ec correspond to the mRNA transcripts comprise of exons 3–4–6, exons 3–4–5 and exons 3–4–5–6, respectively[86] (Fig. I). IGF-IEc (IGF-IEb in rodent) is also called mechano growth factor (MGF) because it is produced when skeletal muscles are subjected to stretch or exercise [70, 86]. Both IGF-IEa and IGF-Eb isoforms are required for the differentiation of C2C12 myoblasts to myotubes[87]. Loss of IGF-IEa is associated with greater reductions in myogenesis than IGF-IEb[87]. Local production of IGF-I requires the E-peptides to drive hypertrophy in growing muscle, since modified IGF-I without the E-peptide can not induce hypertrophy[88]. Treatment of primary human muscle cell cultures with a synthetic MGF-24aa-E peptide increased the proliferative capacity of human myoblasts isolated from neonatal and young adult muscle[70]. However, the peptide did not increase the proliferative capacity of human myoblasts isolated from old adult muscle[70]. As pointed out by Matheny et al[89]., it is not clear whether MGF is present in vivo and its role in SC activation should be ascertained by generating knockout mouse models. Nonetheless, the peptide would be most useful in treating cancer cachexia because it would avoid the potential oncogenic effect associated with mature IGF-I.

Box 3

Other factors and signaling pathways involved in muscle mass maintenance and adaptation

Testosterone

Testosterone is a steroid hormone and an AR ligand that increases lean body mass and reduces fat mass. Myocyte-specific AR ablation results in lower body weights and lean body mass and a conversion of fast toward slow fibers, without affecting muscle strength or fatigue[90]. Testosterone stimulates the proliferation of primary human skeletal muscle cells[1].

Inflammatory pathways

Inflammation has been indicated as the primary cause of muscle wasting during aging and chronic disorders[91]. Among the pathways controlling inflammation, those activating transcription factor nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) play a major pleiotropic role in the modulation of inflammation, cell survival, proliferative responses, and muscle atrophy[92–94]. NF-kB inhibition via inhibitor of nuclear factor kappa-B kinase subunit beta (IKK2) depletion protects against denervation induced atrophy, by maintaining fiber type, size, and strength, increasing protein synthesis, and decreasing protein degradation. Interestingly, IKK2-depleted mice with a muscle-specific transgene expressing a local IGF-I isoform (mIGF-I) showed enhanced protection against muscle atrophy[93].

Myostatin

Myostatin, a secreted protein that belongs to the TGF-β family, inhibits muscle growth and regeneration. Skeletal muscle is the main source of myostatin[95]. Treatment of human myoblasts with myostatin reduces Akt, p70S6 kinase and FoxO1phosphorylation which can be restored by treatment with IGF-I[57]. Skeletal muscle from myostatin knockout mice shows increased Akt protein expression[95]. Interestingly, muscle hypertrophy induced by myostatin inhibition can occur in the absence of *Sdc4* or *Pax7*, both of which are important for SCs activity[96]. It suggested that myostatin inhibition may have beneficial effects in clinical settings in which satellite cells are reduced, such as in sarcopenia. However, myostatin blockade is known to lead to a great increase in muscle mass without increasing muscle force due to mitochondrial depletion [97].

Outstanding questions Box

- What is the master switch for each wasting condition?
- Is specific intervention required for each individual wasting condition and will the addition of IGF-I treatment provides additional benefit?
- Is IGF-I helpful in all types of muscle wasting and to what extend?
- What is the safe dose and duration of IGF-I therapy?
- What is the exact role of different IGF-I isoforms in satellite cell activation, protein synthesis and inhibition of catabolic process?
- In addition to CNTF, what other factors do Schwann cells produce and do they have a role in axon sprouting or satellite cell activation?

Highlights

- IGF-I signaling is important in skeletal muscle maintenance and repair
- IGF-I can reverse various muscle wasting conditions in experimental models
- The potential therapeutic effect of novel IGF-I formulations and biodegradable IGF-I variants must be explored in clinical trials

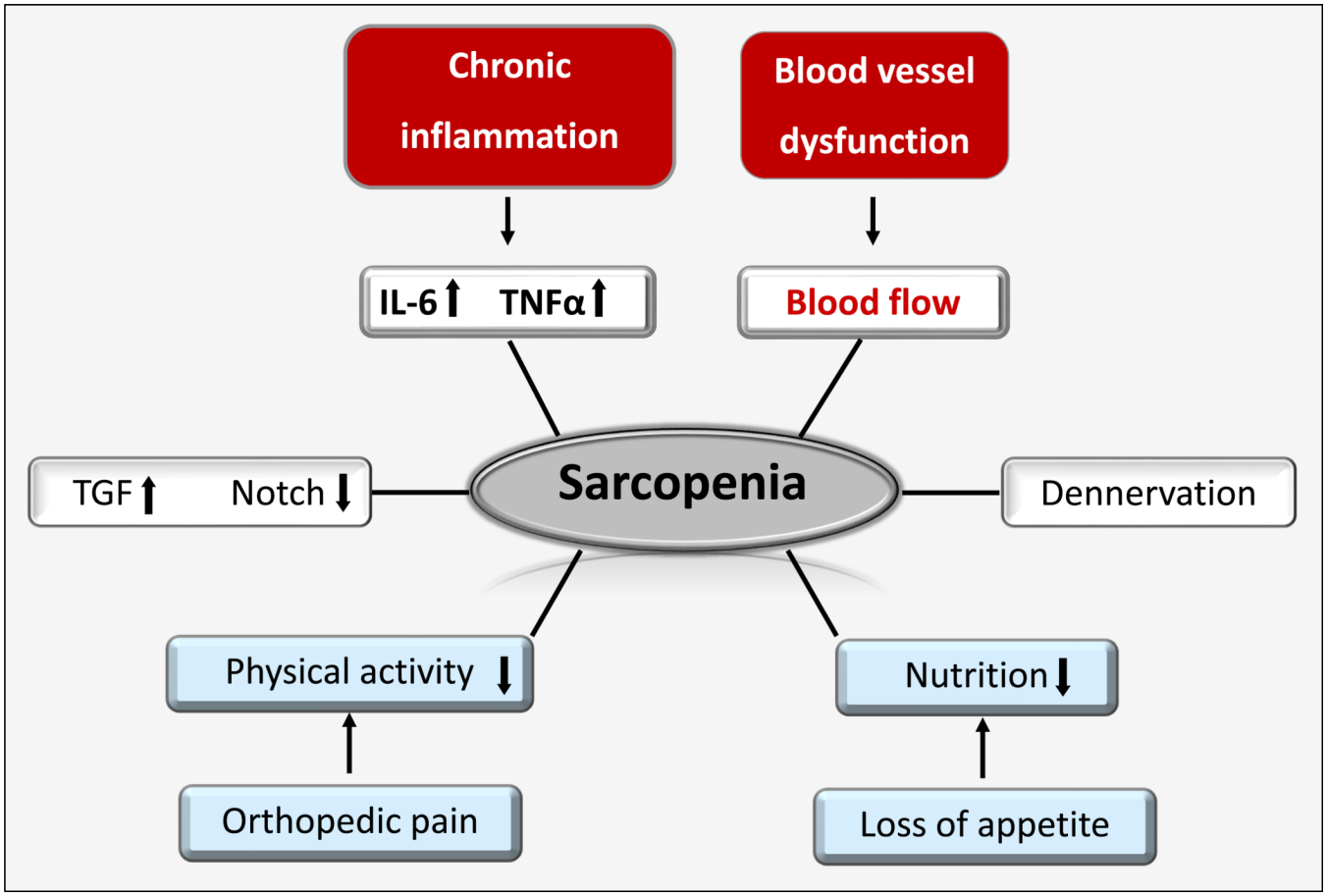

Figure 1. Mechnisms of sarcopenia

Sarcopenia is caused by multiple factors which include the production of IL-6, TNFα as a result of chronic inflammation; reduced blood flow due to blood vessel dysfunction; dennervation; imbalance between TNF and Notch activity; reduced physical activity and loss of appetite.

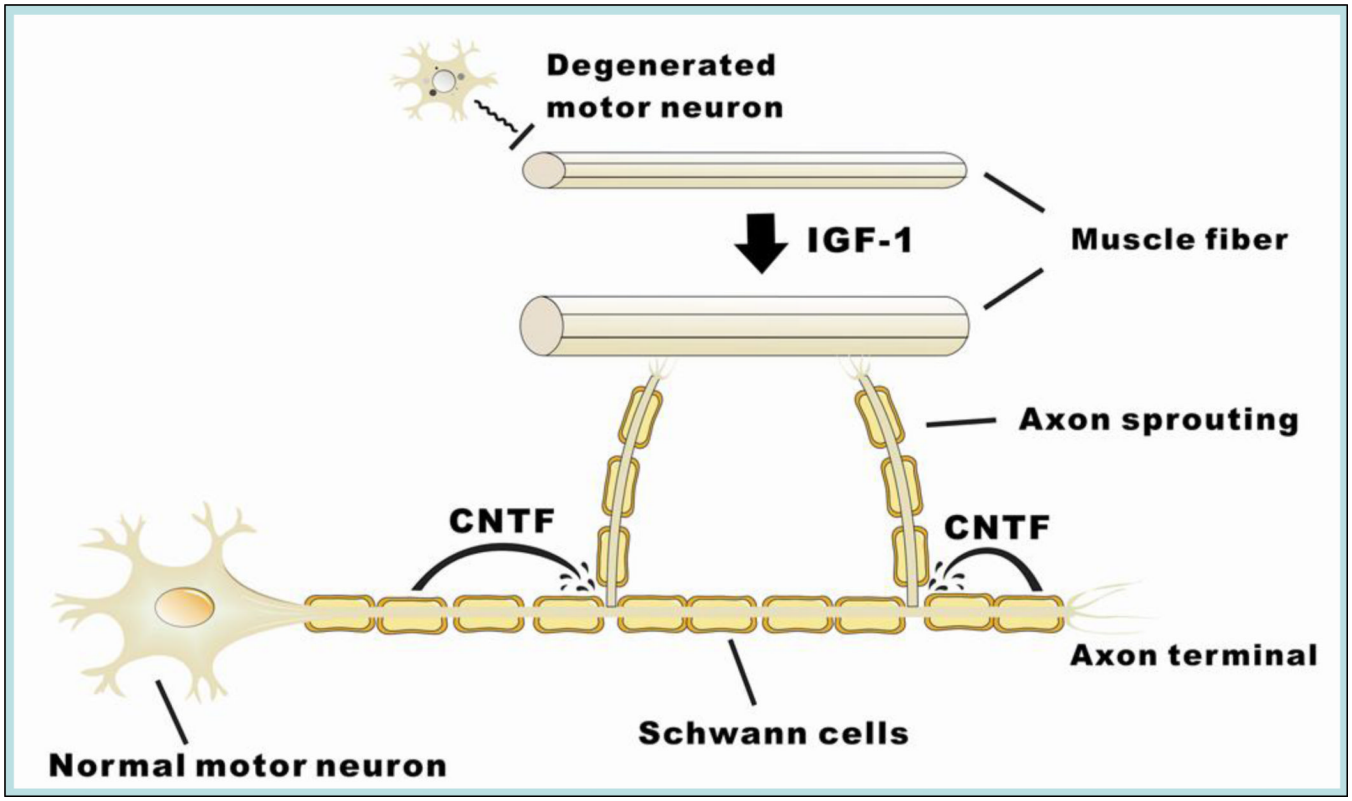

Figure 2. Compensatory axon sprouting for motor neuron diseases

Muscle atrophy associated with neuromuscular diseases is caused by denervation of muscles resulting from degeneration of the motor neurons. IGF-I treatment can induce muscle hypertrophy, but reinnervation of the muscle fibers is accomplished by axon sprouting from remaining intact normal motor neurons. Collateral sprouting requires CNTF which is expressed in Schwann cells surrounding axons.

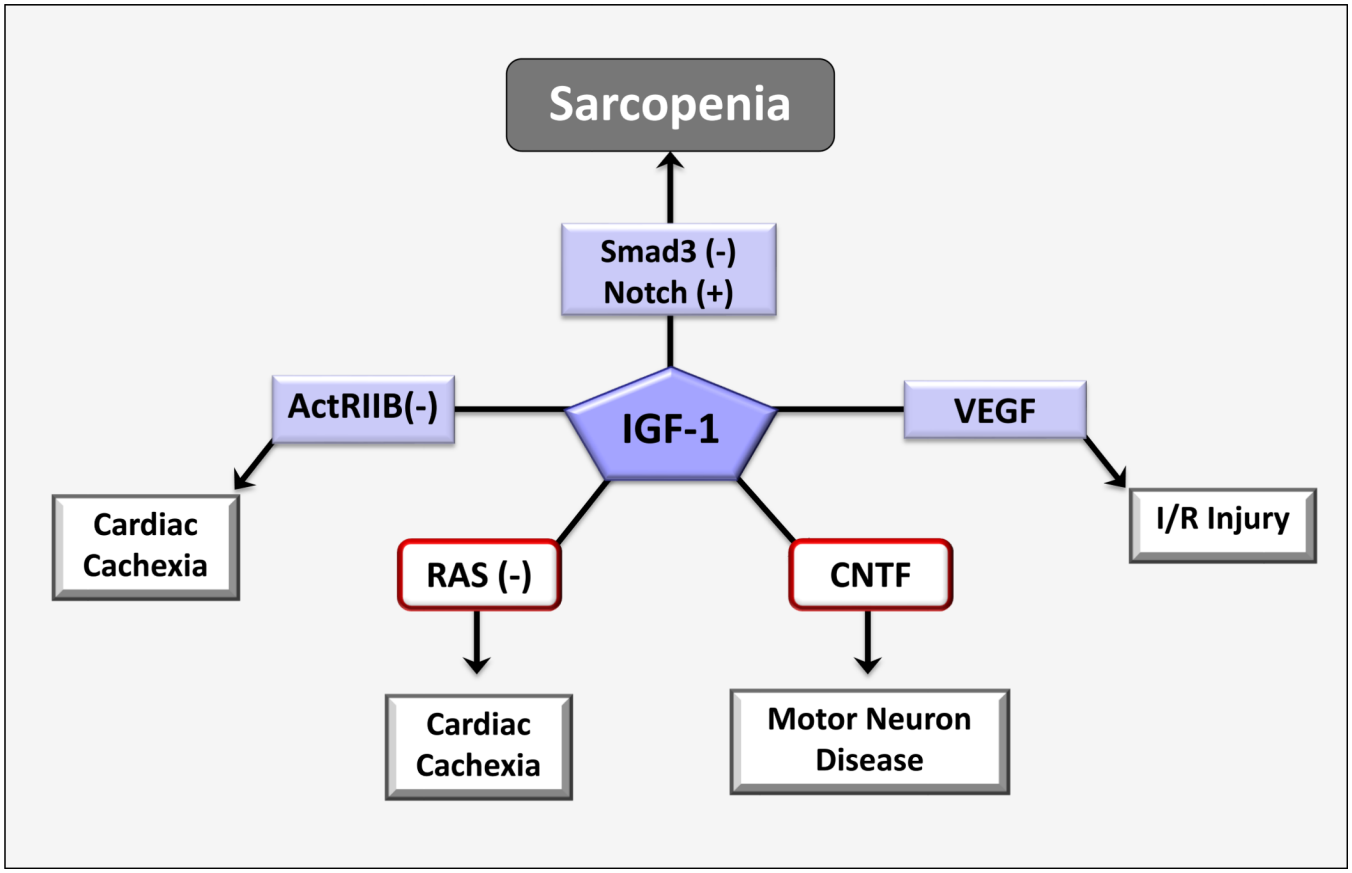

Figure 3. Combination therapy

IGF-I plays a central role in muscle repair and regeneration. Specifically, IGF-I plus inhibitors of activin/myostatin receptor ActRIIB, renin–angiotensin–aldosterone system (RAS) and Smad3 may be beneficial for cancer cachexia, cardiac cachexia and sarcopenia, respectively; whereas IGF-I in combination with stimulators of the Notch pathway, VEGF and CNTF may be a good strategy for treatment of sarcopenia, ischemia reperfusion injury (I/R) and motor neuron diseases, respectively.

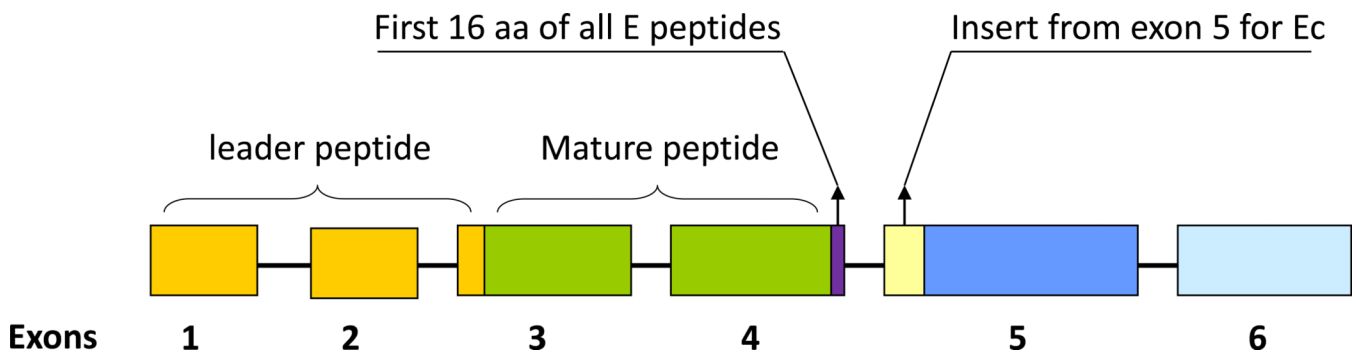

Figure I. BOX 2: IGF-I isoforms

The IGF-I gene has two promoters and six exons. Adapted from Velloso et al[86] with modifications. Exon 1 or 2 encodes the initial amino acids of a leader peptide. Exon 3 encodes the remaining of the leader peptide and a portion of the mature IGF-I peptide. Exon 4 encodes the remaining part of the mature peptide and the first 16 amino acids of the E peptides. The rest of the E peptide is encoded by exon 5 (Eb), exon 6 (Ea) or an insert from exon 5 (49 bp in humans, 52 bp in rodents) spliced onto exon 6 (Ec). IGF-IEc (IGF-IEb in rodent) is also called mechano growth factor (MGF)