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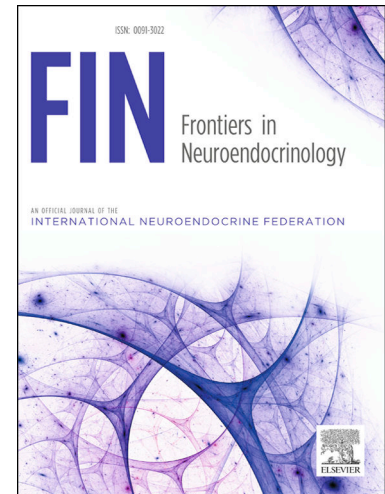
# Insulin-like growth factor 1 signaling in motor neuron and polyglutamine diseases: From molecular pathogenesis to therapeutic perspectives

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**Abstract**

The pleiotropic peptide insulin-like growth factor 1 (IGF-I) regulates human body homeostasis and cell growth. IGF-I activates two major signaling pathways, namely phosphoinositide-3-kinase (PI3K)/protein kinase B (PKB/Akt) and Ras/extracellular signal-regulated kinase (ERK), which contribute to brain development, metabolism and function as well as to neuronal maintenance and survival. In this review, we discuss the general and tissue-specific effects of the IGF-I pathways. In addition, we present a comprehensive overview examining the role of IGF-I in neurodegenerative diseases, such as spinal and muscular atrophy, amyotrophic lateral sclerosis, and polyglutamine diseases. In each disease, we analyze the disturbances of the IGF-I pathway, the modification of the disease protein by IGF-I signaling, and the therapeutic strategies based on the use of IGF-I developed to date. Lastly, we highlight present and future considerations in the use of IGF-I for the treatment of these disorders.

**Keywords**

## 1. Introduction

Insulin growth factor 1 (IGF-I) exerts key and fundamental effects on the development and function of human body organs. IGF-I belongs to the insulin family of peptides along with IGF-II and seven other peptides related to the polypeptide hormone relaxin. Insulin, IGF-I, and IGF-II share a high degree of homology of primary structure and biological actions [1]. Insulin is primarily synthesized as proinsulin by the β-cells of the pancreas, and then cleaved to form mature insulin and peptide C. IGF-I and II are mainly synthesized by the liver, and retain peptide C, which contains an extended carboxy terminus [2]. IGF-I and II are generally considered anabolic factors, with IGF-I increasing cell proliferation, protein synthesis and peripheral glucose uptake [3; 4]. Both IGF-I and II have been shown to be essential during the embryonic development in mouse [5]. IGF-I is involved in governing body growth after birth, whereas the precise physiological function(s) of IGF-II remains an enigma. IGF-I is continuously secreted by the liver into the bloodstream throughout life and functions as a classical circulating hormone in an autocrine and paracrine fashion. IGF-I secretion is regulated by growth hormone (GH) produced by the pituitary and whose receptors are located in the liver. Circulating IGF-I acts as a negative feedback regulator on GH production by targeting both the hypothalamus and the pituitary secretion of GH [6]. The *IGF-I* is a single gene composed of six exons that creates multiple transcripts by alternative splicing, leading to transcription of several tissue-specific isoforms. These tissue-specific isoforms of *IGF-I* can be subdivided into two principal classes: class I consists of the *IGF-I* gene with exon 1 from promoter 1, and class II has a leader sequence encoded by exon 2 from promoter 2. Various factors including exercise-induced muscle damage, prostate or cervical cancer, and aging have been shown to modulate the transcription of the IGF-I splice variants in humans [7; 8; 9; 10]. The turn-over and bioavailability of IGF-I is regulated by the IGF binding proteins (IGFBPs), which protect IGF-I from proteolytic degradation and modulate its availability to the receptors [11]. There are six IGFBPs, and their function is critical to modulate IGF-I and II activity [12]. Among them IGFBP-3 is the most enriched protein that binds to approximately 80–85% of circulating IGF-I [13]

IGF-I and insulin specifically bind to two high-affinity membrane-associated receptors with tyrosine kinase activity, namely the insulin (IR) and IGF-I (IGF-IR) receptors. Most cells of the body express on their surface IR and IGF-IR, which can form both homodimers and heterodimers (IR/IGF-IR hybrids) [14; 15]. Activation of

either IR or IGF-IR evokes similar initial responses within the cell [16]. IR and IGF-IR are tetrameric glycoproteins that consist of two α and two β subunits [17]. IR and IGF-IR show a high structural homology and are composed of a transmembrane domain, a kinase domain, and an extracellular ligand binding domain. Due to this structural and functional homology, insulin and IGF-I can bind to (and activate) both IR and IGF-IR. Nonetheless, insulin has a higher affinity for the IR compared to IGF-I, whereas IGF-I preferentially binds IGF-IR. The IR/IGF-IR hybrids show same affinity for IGF-I than IGF-IR but bind insulin with lower affinity than IR [18]. Once bound to the α subunits of the IR or IGF-IR, IGF-I promotes auto-phosphorylation of the β subunit, which in turn triggers its intrinsic tyrosine kinase activity [19]. The activation of IGF-I tyrosine kinase activity leads to phosphorylation of insulin receptor substrate (IRS) docking proteins (IRS1-4) [20]. These phosphorylation events recruit Src homology-2 (SH2) domain-containing signaling molecules, namely the p85 regulatory subunit of phosphatidylinositol 3-kinase (PI3K). p85 activates both the catalytic subunit of PI3K and the growth factor receptor-bound protein 2 (Grb-2) [21], leading to activation of two major signaling pathways: the PI3K/Akt and the Ras/Raf-1/ERK1/2 pathways.

## 1.1. PI3K/Akt Signaling Cascade

The PI3K/Akt pathway regulates a large number of physiological processes. Upon the activation of PI3K, the subsequent formation of phosphatidylinositol (3,4,5)-trisphosphate and phosphatidylinositol (4,5)-biphosphate (PI3P and PI2P) triggers the binding and recruitment of Akt to the plasma membrane, where Akt is activated upon phosphorylation by 3-phosphoinositide-dependent protein kinase-1 (PDK1) (**Figure 1**) [22; 23]. Active Akt translocates from the plasma membrane to the cytosol and nucleus, where it targets a number of downstream factors involved in survival, proliferation and cell growth, such as transcription factors, pro-apoptotic Bcl-2 family members, and caspases [24; 25; 26; 27]. Dephosphorylation of PI3P and PI2P by the tumor suppressor phosphatase and tensin homolog deleted on chromosome ten (PTEN) antagonizes PI3K and prevents the activation of Akt. Other targets of Akt are forkhead box-O (FoxO) transcription factors, which induce expression of genes involved in protein quality control, such as the ubiquitin proteasome system (UPS) and autophagy. Phosphorylation of FoxOs by Akt promotes their interaction with 14-3-3 in the cytoplasm, which results in nuclear exclusion and degradation by the UPS [28]. In addition, Akt protects cells

from apoptosis by targeting the c-Jun N-terminal kinase (JNK) pathway. The JNK pathway has been shown to be activated in several pathological conditions, including excitotoxicity, trophic factor withdrawal and ischemia [29]. Akt interacts with the JNK interacting protein 1 (JIP1) and inhibits JIP1 from forming active complexes with JNK [30]. Target of rapamycin (mTOR) is a substrate of Akt, which regulates protein synthesis and cell growth. Akt activates mTOR directly through phosphorylation, and indirectly through phosphorylation and inactivation of tuberous sclerosis complex 2 (TSC2), which in turn leads to the inhibition of mTOR via the GTP-binding protein Ras homolog enriched in the brain (Rheb). mTOR can phosphorylate Akt when bound to Rictor in the TORC2 complex, thereby providing a positive feedback along the pathway [31]. Akt has been shown to phosphorylate and inhibit glycogen synthase kinase 3 (GSK-3$\beta$), a kinase involved in several cellular processes such as apoptosis, survival, development, trafficking and transcription [32]. GSK-3$\beta$ may also modulate synaptic plasticity in the central nervous system [33]. Furthermore, Akt controls the transcriptional activity of the nuclear factor-$\kappa$B (NF$\kappa$B), which regulates cellular functions related to immunity and inflammation, by inducing phosphorylation and subsequent degradation of the inhibitor of $\kappa$B (I$\kappa$B) at Ser-32 [34; 35; 36; 37; 38].

## 1.2.   Ras/ERK Signaling Cascade

The adapter protein Src homology-2 domain containing (SHC) binds to IGF-IR in response to phosphorylation of IGF-IR. This in turn recruits Grb2 via its SH2 domains and activates the ERK1/2 signaling pathway (**Figure 1**). SH3 domains mediate the interaction with guanine nucleotide exchange factor son of sevenless (SOS), stimulating the exchange of GDP for GTP at Ras, which then becomes active and recruits the Ser/Thr kinase Raf. Subsequent activation of mitogen activated protein kinase (MEK or MAP2K) leads to phosphorylation (and activation) of ERK1/2 at Thr and Tyr residues, culminating in activation of several transcription factors that control gene expression, such as Ets-like protein-1 (Elk-1) and c-Myc [39]. Within 15 minutes upon activation, ERK1/2 translocates into the nucleus, where it localizes during the entire G1 phase, and can be reversed upon removing the mitogenic stimulus. ERK1/2 must be active until late G1 for successful S-phase entry [40], and its translocation to the nucleus is essential for G1 to S phase progression [41]. ERK1/2 signaling pathway also promotes cell survival by a dual mechanism, comprising the post-translational modification and inactivation of the cell death machinery's components, such as Bcl-xL

[42], and the increased transcription of pro-survival genes [43]. ERK1/2 can affect FoxOs that activate multiple target genes involved in tumor suppression, including *Bim* and *FasL* to induce apoptosis as well as *p27^{kip1}* and *cyclin D* for cell cycle regulation [44]. ERK1/2 phosphorylates FoxO3 at serine residues 294, 344, and 425, resulting in polyubiquitination by MDM2 and degradation by UPS [45]. The crosstalk between Akt and ERK1/2 signaling is at the basis of the pleiotropic effects of IGF-I on different cell types, which highlights the multiple levels of regulation of kinase signaling cascades in response to extracellular signaling.

## 2. Tissue-specific effects of the IGF-I signaling

Activation of the IGF-I signaling has various effects depending on the target tissue, from nervous system to peripheral tissues, such as skeletal muscle. IGF-I has remarkable protective and anti-apoptotic effects in several tissues. For instance, IGF-I has anabolic properties in skeletal muscle and neurotrophic effects in the central nervous system.

### 2.1. IGF-I signaling in the central and peripheral nervous system (CNS and PNS)

Brain levels of IGF-I are elevated during development and reach pick levels in fetal and neonatal brain, to then decrease in adulthood [46]. Nonetheless, some brain regions associated with higher renewal or remodeling maintain certain levels of IGF-I. On the other hand, IGF-IR are widely expressed in the brain and show more stable levels of expression from development to adulthood. The low rates of IGF-I expression in the adult brain together with the stable expression of IGF-IR through life and the fact that serum IGF-I can cross the blood brain barrier, underlie the importance of paracrine functions of IGF-I during adulthood. IGF-I is essential for normal growth, development, neuronal survival, myelin sheath synthesis, astrocyte function, vessel growth, neuronal excitability, and oligodendrogenesis [47; 48; 49; 50; 51; 52; 53; 54]. As in many other tissues, IGF-I functions in the brain in an autocrine and paracrine manner. Circulating IGF-I, 70% of which coming from liver, has been proposed to cross the blood brain barrier through two processes: one takes place at the choroid plexus by transcytosis involving IGF-IR and low-density lipoprotein receptor-related protein 2 (LRP2) transport protein; the second one is linked to neuronal activation, which induces the transportation of IGF-I in a LRP1-dependent process [55; 56]. In an autocrine fashion, IGF-I is  produced by all cell types of the brain. Importantly, after brain injury IGF-I is

highly synthesized by reactive microglia, whereas neurons and astrocytes overexpress IGF-IR, suggesting, together with changes in various IGFBPs levels, a potential defense mechanism to preserve the neural tissue [57; 58; 59; 60; 61; 62; 63]. IGF-IR are widely distributed in different brain areas, particularly in the circumventricular organs, choroid plexus, hypothalamus, cerebellum, and olfactory bulb [64; 65]. IR/IGF-IR hybrids are also expressed in neurons and glia, but not in oligodendrocytes [66] and represent more than 50% of the receptor dimers in the brain [67]. The physiological significance of these hybrids in the brain is not well understood, but it is generally accepted that they decrease insulin signaling as they exert lower affinity for insulin than for IGF-I [68]

Development of mouse models of IGF-I and IGF-IR haploinsufficiency, complete depletion and overexpression has been critical to understanding the role of IGF-I in the brain. Mice specifically lacking the neuronal IGF-IR show microcephaly, growth retardation and smaller body size, and behavioral deficits similar to those observed in human patients [49; 51]. The reduction in brain size is due to decreased soma size of projection neurons, dendritic length, myelination, branching and synapse formation [69; 70]. Brain functionality is also compromised in IGF-I null mice, with downregulation and mislocalization of glucose transporter GLUT4 and decreased GSK-3β activation and glycogen storage, which leads to a misutilization of neuronal glucose and impaired growth [71]. Moreover, clinical studies have shown that point mutations in both the *IGF-I* and *IGF-IR* genes result in decreased IGF-I signaling, microcephaly and postnatal growth impairment, and frequently significant delays in psychomotor function and hearing loss [72; 73; 74; 75; 76]. Accordingly, brain overexpression of IGF-I produces macrocephaly, and mice overexpressing IGF-I in all tissues have increased brain growth postnatally [77; 78]. Thus, these observations support the idea that IGF-I is essential for the development and organization of the CNS.

IGF-I modulates brain function not only during development, but also in the adulthood. IGF-I is an important modulator of adult hippocampal neurogenesis, which is linked to learning and memory processes [79; 80; 81]. IGF-I influences neuronal plasticity and is implicated in the control of long-term potentiation (LTP), learning and neuronal replacement in the hippocampus [82]. IGF-I increases astrocyte intercellular gap junctional communication [83], promotes and maintains dendritic arborization [70], and regulates the rate of neurogenesis in a dose-dependent manner and increases oligodendrogenesis [83]. Together with the brain-derived neurotrophic factor (BDNF)

and the vascular endothelial growth factor (VEGF), IGF-I is a key factor in the neurobiology of exercise, and adult neurogenesis is regulated, among other factors, by physical activity [84]. Exercise has salutary effects on learning and memory by modulating the energy maintenance and synaptic plasticity. *IGF-I* gene expression in hippocampal neurons and IGF-I plasma levels are increased in response to exercise [85; 86], and it has been shown that serum IGF-I mediates exercise-induced neurogenesis through Akt [87; 88]. Indeed, intrahippocampal injections of anti-IGF-I antibodies prevented the beneficial effects induced by exercise on learning and plasticity [85].

Aging is often associated with cognitive and functional decline, dementia-related pathologies and neurodegenerative diseases. Although the role of IGF-I in the aging brain remains unclear, it is clear that its secretion levels decline with age [89]. Intriguingly, downregulation of IGF-I levels has been associated with both aging and anti-aging effects, suggesting that IGF-I may improve some aspects of healthy aging, but it may be detrimental for others. For example, decreased IGF-I levels throughout life increased life span but accelerated the age-related cognitive dysfunction in several model systems [90; 91; 92; 93; 94; 95; 96; 97], while other studies showed improvement in memory, learning and cerebral vasculature [98; 99; 100]. In humans, several works linked the down-regulation of the IGF-I pathway to longevity [101], while others showed an association between lower IGF-I levels and better cognition, or no association [102]. Partial loss-of-function mutations in the IGF-IR gene was prevalent among centenarians, and the downstream effector FoxO3A variant was associated with human longevity [103; 104; 105; 106]. Regarding cognitive functions, low levels of serum IGF-I have been associated with reduced processing capacity, verbal skills and fluid intelligence [107; 108; 109]. Two of these studies were conducted in older men and another one in a sex-mixed population. Importantly, effects of IGF-I seem to be sex-specific, having different impact overall lifespan, health, and pathology. Young and middle-aged women have higher serum IGF-I concentration than age-matched men, but this relationship turned to be inverted with aging [110]. Lower levels of circulating IGF-I correlated with survival in nonagenarian women and with better cognitive performance in women with exceptional longevity, without affecting neither muscle mass nor function [111; 112]. Increased lifespan in female animals was also observed in models of IGF-IR haploinsufficiency [113; 114; 115]. On exercise-induced neuroplasticity, females showed greater improvements in cognitive function after aerobic training than males [116], but no correlation was found between peripheral

levels of IGF-I in females and this sex-specific improvement [117]. Brain levels of IGF-I were not measured. These differences in sex-specific influence of IGF-I in lifespan and health status in aging could be explained by the modulation of sex hormones. Then, as sexual hormones and IGF-I are differentially secreted in males and females, from development to adulthood, these interconnected effects are difficult to unravel. Sexual dimorphism modulates the development and function of the brain. For example, during male and female development, differential time-course changes in IGF-I expression are observed. Pick of maximum expression of IGF-IR in the male rat developing cerebellum occurs in the first postnatal week, while in females this pick occurs in the second week of postnatal development [118]. In male rats, right hippocampus expresses maximum IGF-IR levels in the first week, whereas left hippocampus during the second week. IGF-IR pick expression is reached in both hemispheres during the first week in females [119]. At the molecular levels, estrogens can regulate IGF-IR expression and dimerization, and IGF-I can activate estrogen receptors without the presence of estradiol [120; 121; 122]. Several neuroprotective properties seem to be overlapping between estrogens and IGF-I [123; 124]. Dopaminergic neurons from *substantia nigra* express both estrogen receptors β and IGF-IR [125], and both estrogen and IGF-I are neuroprotective after excitotoxic lesions of the nigrostriatal dopaminergic pathway. The inhibition of IGF-IR blocked the beneficial effects of both IGF-I and estrogens [126]. The IGF-IR blocking abolished the neuroprotection exerted by estrogens in ischemic stroke [127], and the improvement of memory in aging ovariectomized animals by estrogens [128]. In the same way, the neuroprotection exerted by IGF-I in hilar neurons from hippocampus is inhibited by blocking estrogen receptors [129].

These observations show that IGF-I signaling has remarkable but still not well addressed roles in physiological conditions, which seem to be sex-specific, spanning from growth to development and cell homeostasis maintenance in the adulthood.

## 2.2. IGF-I signaling in skeletal muscle

Circulating IGF-I plays an important role on skeletal muscle regeneration [130; 131; 132]. Muscular isoforms of *IGF-I* (*mIGF-I*) are produced locally by skeletal muscle in response to tension and stretching stimulation [133; 134; 135]. The *mIGF-I* isoforms produced by alternative splicing are IGF-IEa and IGF-IEb, and their expression is regulated by different stretching and loading stimuli in skeletal muscle

[136]. IGF-IR are extensively expressed in skeletal muscle, and interestingly, IGF-IR/IR hybrids represent the major form of IGF-IR [67].

Adult muscle stem cells are known as satellite cells and have a remarkable capacity to respond to growth, muscle training, and injury. This small population of cells is located between the basal lamina of the muscle and the sarcolemma of myofibers [137], and it represents the principal source of replenishing cells for the skeletal muscle fibers [138]. Following injury and influenced by growth factors, satellite cells reenter the cell cycle, culminating in myofiber formation and regeneration of skeletal muscle. In response to hypertrophic signals in skeletal muscle, IGF-I is upregulated and promotes myoblast proliferation, differentiation, and fiber formation, both during normal growth and upon muscle injury [139; 140; 141]. Muscle damage induces the expression of the IGF-I isoform mechano growth factor (MGF), followed by that of the calcium-dependent cell adhesion molecule and marker of satellite cells, M-cadherin. In this process, MGF may be the initial IGF-I isoform that triggers the activation of satellite cells, followed by the later expression of IGF-IEa to maintain protein synthesis [142].

Aging is one of the most important factors that influences the efficiency of skeletal muscle regeneration. Aged rats and humans have reduced IGF-I serum levels [143; 144]. Local administration of IGF-I to atrophied muscles of aged rats resulted in significant increases in muscle mass and satellite cell proliferation [140]. Also, in senescent mice the overexpression of mIGF-I maintains the integrative capacity of skeletal muscle, while prolonging its regenerative properties, without entering the circulation or producing hypertrophy of other tissues. This implies that mIGF-I acts locally to exert its protective role [145]. It seems that the effects of IGF-I on muscle fiber formation and hypertrophy occur differently through the two main cellular pathways activated by IGF-I. Through the Ras/ERK signaling pathway, IGF-I affects fiber composition without changing the muscle fiber size [146]. On the other hand, phosphorylation of Akt and subsequent activation of mTOR and p70S6 kinase result in new protein synthesis, hypertrophy and inhibition of the key ubiquitin ligase atrogin-1 by inactivating FoxOs [147]. The anabolic and hypertrophic effects of IGF-I in skeletal muscle imply that this growth factor may have therapeutic effects in aging and age-related disorders involving loss of muscle mass and force.


## 3. Role of IGF-I in diseases of the nervous system

The strong neuroprotective and neurotrophic effects of IGF-I in the CNS make it a suitable candidate for therapy development for diseases of the nervous system. The role of IGF-I in neurodegenerative diseases, such as Alzheimer's disease and Parkinson's disease, has already been discussed elsewhere [79; 148]. Here, we will focus on the involvement of the IGF-I pathway in motor neuron and polyglutamine diseases. After providing key information on these disorders, we will describe three aspects that link IGF-I signaling to the pathogenesis of such neurodegenerative diseases (**Figure 2**). First, we will describe how alterations of IGF-I signaling, which happen very often in neurodegenerative diseases, contribute to disease pathogenesis. Second, we will revise evidence showing how activation of the IGF-I pathway leads to the modulation of several cellular kinases, phosphatases, and other enzymes, which in some cases modify the disease-related proteins at the post-translational level. These post-translational modifications may have key impacts on the metabolism and toxicity of the disease proteins. Third, we will review the literature in support of IGF-I protective effects in various neurological conditions.

### 3.1. Motor neuron and polyglutamine diseases

Spinal muscular atrophy (SMA) is characterized by the degeneration of lower motor neurons, which leads to symmetric and proximal skeletal muscle atrophy and weakness [149]. The incidence of disease is 1/10,000 live births. SMA is inherited in an autosomal recessive manner with different degrees of severity and is classified based on age of onset and the level of motor dysfunction. Type I is the most severe form of SMA, with symptoms manifesting within six months of age and death of patients occurring within two years. Type II and III manifest between 6-18 and after 18 months of age, respectively, and type IV is an adult onset form with very mild symptoms. Finally, type 0 SMA has very severe symptoms and early neonatal death [150; 151]. SMA is caused by loss-of-function mutations in the gene coding for survival of motor neurons (*SMN*) [152]. Humans have two *SMN* genes, one telomeric (SMN1), the other centromeric (SMN2). The *SMN1* gene is transcribed and translated into the full-length protein. A silent C to T mutation at position 840 in the *SMN2* gene leads to the skipping of exon 7 in about 85% of transcripts, which in turn generates a truncated protein that is non-functional and rapidly degraded [153; 154; 155]. Typically, people have two copies of the *SMN1* gene, while the *SMN2* gene copy number varies in the population. As all SMA patients have mutations in both copies in the *SMN1* gene, the different degree of

severity of SMA depends on the levels of full-length protein derived from the *SMN2* gene. Multiple copies of the *SMN2* gene is associated with less severity and late onset of SMA.

Amyotrophic lateral sclerosis (ALS) is a devastating motor neuron disease caused by the selective and progressive loss of cortical, bulbar and spinal motor neurons, which results in irreversible paralysis, speech, swallowing and respiratory malfunctions, and eventually death of patients typically in between 1-5 years from disease onset [156]. Age of onset is around 40-60 years with incidence of disease being 1-2/100,000. About 90% of patients are sporadic (sALS) and 10% are familial (fALS), having predominantly autosomal dominant inheritance, even though autosomal recessive forms have also been described. Several genes have been linked to sporadic and familial ALS. Despite intense research efforts, effective therapeutic options are absent.

Polyglutamine (polyQ) diseases are a family of nine neurodegenerative disorders caused by exonic expansions of CAG trinucleotide repeats, encoding glutamine, in nine unrelated genes [157; 158]. The polyQ disease family includes spinal and bulbar muscular atrophy (SBMA), Huntington's disease (HD), dentatorubral-pallidoluysian atrophy (DRPLA), and six types of spinocerebellar ataxia (SCA). PolyQ diseases share several features, such as neuronal vulnerability, protein misfolding and aggregation, as well as a late-onset exordium.

Spinal and bulbar muscular atrophy (SBMA), or Kennedy disease, is an X-linked, adult onset neuromuscular disease associated with skeletal muscle atrophy and the loss of motor neurons in the spinal cord and brainstem. In the initial phase of the disease, patients experience muscle cramping, tremors and fatigue, followed by muscle weakness and atrophy [159]. The disease affects 1–2/100,000 male individuals. SBMA is caused by polyQ expansions in exon 1 of the androgen receptor (*AR*) gene [160]. SBMA fully affects males, due to polyQ-AR toxicity being triggered by binding to androgens [161]. Binding to testosterone leads to the translocation of AR to the nucleus, where AR exerts its function as a transcription factor, up- or down-regulating androgen-responsive genes.

Spinocerebellar ataxia (SCA) types 1, 2, 3, 6, 7, and 17 are caused by polyQ-expansions in the genes coding for Ataxin-1, Ataxin-2, Ataxin-3, α1A subunit of the neuronal P/Q-type voltage-gated calcium channel, Ataxin-7, and TATA binding protein, respectively. At early stages of disease, SCA patients present with a gait imbalance followed by appendicular ataxia, dysarthria, and visual problems, such as focusing,

diplopia and saccades. In some case difficulty to swallow and breathe is also observed [162]. Ataxia results from progressive degeneration of cerebellar Purkinje cells along with neurons in the brainstem and spinocerebellar tracts. Aside from SCA6, which is typically considered a "pure cerebellar" ataxia, the other SCAs linked to expanded polyQ display substantial brainstem involvement. Cortical degeneration contributes to clinical features especially in SCA17, and retinal degeneration is characteristic of SCA7. Spinal cord and peripheral nerve involvement are more common to all the polyQ-linked SCAs.

Huntington's disease (HD) is an inherited neurodegenerative disorder caused by polyQ expansions in the gene coding for huntingtin (HTT) [163]. HD patients exhibit a range of motor symptoms, including chorea and bradykinesia, as well as progressive cognitive decline. In addition to these core clinical symptoms, several other abnormalities are frequently seen in HD patients, including weight loss, skeletal muscle wasting, osteoporosis, and testicular abnormalities. After disease onset, the average lifespan is approximately 10–20 years. Although HTT is expressed ubiquitously, the disease manifests with the selective degeneration of striatal, medium-sized spiny neurons, and at later stages of disease, cortical neurons and interneurons [164; 165]. The pathogenic mechanisms underlying neuronal loss remain elusive. HD is a highly complex and multifactorial disease that comprises excitotoxicity, oxidative stress, protein misfolding, alterations of calcium homeostasis, transcription, intracellular signaling, axonal transport and synaptic transmission, impairment in energy metabolism and mitochondrial defects.

### 3.2. Altered IGF-I signaling in motor neuron and polyglutamine diseases

IGF-I signaling is altered in motor neuron diseases, such as SMA and ALS, and polyQ diseases, such SBMA, SCA1, 3, and 7, and HD. The expression of IGF-I and IGFBP-3 was decreased in SMA mice, resulting in reduced serum IGF-I levels [166; 167]. Interestingly, an axonal-specific SMN isoform has been shown to regulate the expression of IGF-I, indicating that IGF-I expression in neurons is controlled by SMN [168]. The levels of IGF-I and IGFBPs in the serum, cerebrospinal fluid and spinal cord have been extensively analyzed in ALS patients, giving in some cases to conflicting results, possibly due to the high degree of variability among patients. There is evidence showing that in ALS patients the levels of GH, IGF-I, IGFBP-2, and IGFBP-3 are normal in serum and decreased in cerebrospinal fluid, whereas those of insulin are

decreased in both serum and cerebrospinal fluid [169; 170; 171; 172]. Interestingly, GH secretion was reduced in ALS patients, yet with normal or higher IGF-I levels [173; 174], as well as in mice carrying a glycine 93 to alanine mutation in the gene coding for superoxide dismutase 1 (SOD1$^{G93A}$) [175]. This occurred alongside dysfunctional pulsatile GH secretion, decreased pituitary GH content, decreased circulating levels of IGF-I, and decreased α-subunits of IGF-IR expression in skeletal muscle and the lumbar spinal cord. These observations suggest that there is a global disruption in the GH-IGF-I axis during the late stages of disease in SOD1$^{G93A}$ mice. In addition to measuring total IGF-I, another factor that needs to be taken into account is its bioavailability.  As a matter of facts, the levels of free IGF-I, which is the bioactive form of IGF-I, in the serum of sporadic ALS patients correlated with disease severity and were decreased in the ventral spinal cord, even if significantly enhanced in the cerebrospinal fluid [171; 176]. Interestingly, there seems to be an increase in the binding sites of IGF-I and IGF-II, but not insulin, in the spinal cord autopsy specimens from ALS patients [177; 178]. Others reported that IGF-I and insulin levels were decreased in serum, yet normal in the spinal cord, rather the expression of specific IGFBPs and IGF-IR was increased in ALS spinal motor neurons [176; 179]. On the other hand, the serum IGF-I levels were found to be increased, while IGFBP-1 levels be decreased in slowly progressive ALS patients, suggesting a correlation between IGF-I bioavailability and disease duration [180]. As reflected in a lower concentration of the regulatory protein IGFBP-1, a possible decrease in total IGF-I binding capacity suggests an increased bioavailability of IGF-I in surviving ALS patients. This lends support to the concept of a homeostatic response to neurodegeneration. Therefore, even if these studies show different results in some cases, which may mirror the high degree of variability among patients, an increase in IGF-I signaling is perhaps a compensatory response with a positive outcome on disease progression and duration.

In mouse models of SCA1 and SCA7, microarray analysis revealed a down-regulation of IGFBP-5 at early stage of disease in the cerebellum, a phenomenon that was progressive and limited to vulnerable brain regions, with no changes in unaffected brain regions, such as cortex [181]. IGFBP-5 was downregulated in granule cells in a non-cell-autonomous fashion, as it occurred in a SCA1 mouse model in which mutant protein was expressed selectively in Purkinje cells, and correlated with increased activation of the IGF-IR and the downstream effectors, Akt and ERK, which could be the consequence of increased IGF-I bioavailability. Aberrant Akt activation was also

detected in SCA1 cells and in the cerebellum of SCA1 transgenic mice compared to controls [182]. Altered insulin sensitivity and insulin resistance were observed in SCA1 and SCA3 patients [183; 184], as well as animal models of SCA1 and SCA7 [181]. Although the serum levels of IGF-I do not change in SCA3 patients versus control individuals, IGF-I levels were inversely correlated with the volume of medulla oblongata and basis pontis [183].

IGF-I levels have been shown to be altered in HD. HTT positively regulates IGF-I expression, and the age-related decrease in expression of polyQ-HTT was associated with reduced production of IGF-I in animal models as well as in the caudate of HD patients [185]. However, the levels of circulating IGF-I were reported to be elevated in the serum of HD patients, which correlated with greater cognitive decline in HD patients [186]. The activity of Akt is altered in HD. Prior to neurodegeneration, the predominant Akt species detected was an inactive caspase 3 proteolytic cleavage product [187; 188]. On the other hand, total Akt levels were increased, and the ratio active/total Akt was decreased in cells derived from HD patients [188], as well as in a knock in mouse model of HD [189]. SGK levels are also altered [190]. This evidence shows that IGF-I signaling is altered in HD.

Importantly, IGF-I signaling has been shown to be altered in skeletal muscle and other peripheral organs, implying cell-autonomous and non-cell-autonomous mechanisms. IGF-I signaling is altered in the muscle of SMA patients [191]. SMA type I patients showed reduced levels of eukaryotic translation initiation factor 4E-binding protein 3 (eIF4EBP3) and Fbox32 and elevated levels of IGF-IR and FoxOs. SMA type III patients also showed reduced expression of genes belonging to the IGF/PI3K/Akt pathway, while mTOR was overexpressed. Therefore, increased expression of mTOR in SMA type III compared to type I may enhance the rate of protein synthesis and lead to compensatory muscle hypertrophy with a milder phenotype. In ALS patients, the expression of IGF-I and the IGFBP-3, 4, and 5 was decreased, whereas that of the β-subunits of IGF-IR was increased in skeletal muscle [192]. Another important aspect related to IGF-I signaling in ALS muscle is that Akt phosphorylation is reduced in the muscles of ALS patients and SOD1$^{G93A}$ mice, further suggesting that altered IGF-I signaling contributes to ALS muscle atrophy [193]. Release of IGF-I by microglia expressing SOD1$^{G93A}$ was decreased compared to normal cells [194]. Recently, decreased expression of IGF-I and increased expression of IGFBP-1 has been reported in the liver of SOD1$^{G93A}$ mice [195]. Because abnormalities in the liver were also found

in ALS patients [196], altered IGF-I axis may contribute to disease pathogenesis. The IGF-I signaling pathway is altered in the skeletal muscle of SBMA knock-in mice and patients [197]. Akt and mTOR were aberrantly phosphorylated in the muscles of SBMA mice. Notably, mTOR activation correlated with increased protein synthesis concomitant to increased protein degradation, suggesting enhanced protein turnover. No alteration of the IGF-I pathway was observed in the spinal cord in SBMA mice. These results suggest that enhanced activation of IGF-I signaling occurs only in skeletal muscle and may represent a compensatory effect to muscle atrophy in the initial phase of disease, which could become detrimental as disease progresses.

## 3.3. Post-translational modification of the disease-related proteins by IGF-I signaling

There is no evidence of post-translational modifications of SMN occurring upon activation of IGF-I signaling. Moreover, it is still not known whether activation of the IGF-I pathway directly modifies any of the disease proteins linked to ALS. For instance, several ALS-linked proteins have serine/threonine residues within potential Akt consensus sites, raising the intriguing possibility that the IGF-I pathway alters disease pathogenesis through direct modification of the disease protein [198]. Different is the case of AR. Others and we have previously shown that AR is a direct target of the IGF-I signaling [198]. Normal AR [199] and polyQ-AR [200] are phosphorylated by Akt at serine 215 and serine 792 (**Figure 2**). Phosphorylation of polyQ-AR by Akt blocked binding to androgens, resulting in protein degradation through the proteasome [200; 201]. Importantly, phosphorylation of the disease protein by Akt prevented androgen-induced events implicated in disease pathogenesis [200], and it was mutually exclusive with arginine methylation at the Akt consensus sites [202]. Normal AR was shown to structurally and functionally interact with several effectors of the IGF-I/Akt pathway. For instance, GSK-3β phosphorylated normal AR in the amino-terminal domain and repressed transactivation in cultured cells [203]. This evidence reveals that AR is a direct target of the IGF-I signaling, and that post-translational modification of polyQ-AR impacts disease pathogenesis, thereby offering therapeutic opportunities.

Several proteins linked to SCA either have been shown to be modified by kinases modulated by IGF-I or have potential phosphorylation sites for such enzymes [198]. Ataxin-3 was phosphorylated by GSK-3β at serine 256, and phosphorylation at this site reduced aggregation (**Figure 2**) [204]. The SCA1 and SCA6 disease causing proteins

have Akt consensus sites, and Ataxin-1 has been shown to be phosphorylated at serine 776 by PKA with major effects on toxicity [205]. While phosphorylation of Ataxin-1 regulates protein stability, it remains to be established whether the α1A subunit of the neuronal P/Q-type voltage-gated calcium channel is phosphorylated in SCA6 and what is the functional consequence of this post-translational modification in disease pathogenesis.

Experimental evidence demonstrated that HTT is directly modified by the IGF-I signaling. Akt and SGK have been shown to phosphorylate normal and polyQ-HTT at serine 421 (**Figure 2**) [187; 190]. In normal mice, the degree of HTT phosphorylation at serine 421 has been observed to be higher in the striatum as compared to other brain regions, and it was altered by polyQ expansion [206]. Aberrant phosphorylation of polyQ-HTT resulted in altered anterograde-retrograde transport of vesicles, with phosphorylated HTT promoting anterograde transport, and non-phosphorylated HTT promoting retrograde transport [207; 208]. The mechanism through which polyQ expansions alter HTT phosphorylation involved excitotoxic N-methyl-D-aspartate receptor (NMDAR) stimulation [209]. Serine 421 phosphorylation was regulated by the protein phosphatases 1 and 2A (PP1 and PP2A), whose activity is altered in HD. This suggests that imbalance between kinase and phosphatase activity is likely to result in decreased polyQ-HTT phosphorylation and toxicity [210].

### 3.4. Does IGF-I signaling modify motor neuron and polyQ diseases in vivo?

Based on the evidence reviewed above, which links diminished IGF-I signaling to disease pathogenesis together with a direct effect on the disease-related proteins in some cases, IGF-I has largely been tested in genetic, preclinical and clinical studies to assess its therapeutic potential in motor neuron and polyQ diseases.

### 3.4.1. Genetic manipulation of IGF-I signaling

Genetic manipulation of IGF-I levels provided evidence that enhancement of IGF-I signaling in SMA, ALS, and SBMA has beneficial effects *in vivo*, even if the effect seems to be dependent on the target tissue and the IGF-I isoform expressed. Indeed, genetic manipulation of human IGF-I obtained by crossing the SOD1[G93A] mice with mice that overexpress IGF-I selectively in either the CNS [211] or skeletal muscle [212] failed to show any effect on phenotype [213]. However, ectopic expression of a muscle-specific isoform of IGF-I selectively in skeletal muscles of mice modeling SMA

[214], ALS [215], and SBMA [201] remarkably ameliorated phenotype and extended lifespan, indicating that the muscle-specific isoform of IGF-I modifies disease, and suggesting that skeletal muscle may be an important target tissue for therapy development. In the case of SBMA, activation of the IGF-I/Akt pathway increased polyQ-AR phosphorylation at serines 215 and 792, which in turn mitigated polyQ-AR nuclear accumulation in the muscles of SBMA mice.

### 3.4.2. Preclinical assessment of IGF-I

Experimental and preclinical evidence supports the idea that IGF-I has therapeutic potential. Indirect evidence that IGF-I may have beneficial effects in SMA came from the observation that intervention to increase the expression of SMN in peripheral tissues in SMA mice ameliorated phenotype and increased expression of IGF-I, suggesting that activation of IGF-I signaling in peripheral tissues attenuates the SMA phenotype [166]. Using adeno-associated viral (AAV) vectors in mice modelling type III SMA, the administration of IGF-I into the deep cerebellar nucleus resulted in increased expression of IGF-I in the spinal cord and reduced motor neuron death [216]. However, this strategy failed to ameliorate motor performance and muscle pathology, due to the fact that the rescued motor neurons did not properly innervate the muscles. AAV-mediated systemic delivery of IGF-I administered by intravenous injection in SMA mice resulted in increased hepatic transduction and secretion of IGF-I, which correlated with a significant reduction in motor neuron death, muscle degeneration, and cardiac atrophy, together with increased lifespan and improved motor function [217]. Therapy based on activation of IGF-I signaling combined with a trans-splicing RNA to improve expression of full length SMN from the *SMN2* gene have been proven to be beneficial in a severe mouse model of SMA [218]. Treatment of SMA mice with loganin, an anti-diabetic drug with neuroprotective effects, resulted in activation of the IGF-I pathway with protective effects in both motor neurons and skeletal muscle [219].

The preclinical potential of IGF-I signaling has long been explored in the last decades in ALS animal models. Implantation of neural stem cells in ALS mice attenuated disease manifestations, and this effect was associated with increased IGF-I signaling [220]. Treatment of ALS mice with polyethylene glycol-modified IGF-I ameliorated disease manifestations [221]. Delivery of IGF-I to the CNS of ALS mice, rats and patients reduced motor neuron loss and ameliorated phenotype [222; 223; 224; 225] . Interestingly, in ALS rats IGF-I was effective only in males, indicating a gender

effect on the outcome of IGF-I treatment in ALS pathogenesis. It is of notice that intrathecal administration of IGF-I fused to the tetanus toxin fragment C failed to modify disease progression and survival in SOD1-G93A mice [226]. Intramuscular delivery of IGF-I with adeno-associated and lentiviral virus injections ameliorated phenotype of ALS mice [227; 228], suggesting that the effect of IGF-I on both muscle and spinal cord may be required to modify phenotype. Intramuscular delivery of MGF also reduced muscle pathology and motor neuron loss [229]. MGF has been shown to increase the number of muscle progenitor cells in primary cell cultures derived from ALS patients [230]. Exercise stimulates the production of specific IGF-I isoforms, including MGF [231], and consistent with a protective role of these isoforms in models of muscle injury, combined treatment of ALS mice with exercise had a remarkable beneficial effect on phenotype [232]. AAV9-mediated delivery of human IGF-I to the CNS, intramuscularly or intravenously of ALS mice delayed disease onset, ameliorated motor function and reduced inflammation and the neuropathological signs throughout the brain and spinal cord [233; 234; 235]. Intranasal delivery of IGF-I to SCA1 transgenic mice results in improved motor function and histopathology [236]. Subcutaneous injection of IGF-I to a mouse model of SCA6 partially restored cerebellar function without increasing the survival of Purkinje cells [237].

An alternative strategy to the use of viruses to deliver IGF-I is a pharmacological approach. Treatment of severe SMA mice [167] and SBMA mice [238] with IPLEX, which combines human recombinant IGF-I complexed to IGFBP-3, attenuated motor dysfunction. However, in SMA mice IPLEX had no effect on the survival and body weight of the animals. Treatment of SBMA mice with IPLEX increases polyQ-AR phosphorylation by Akt and reduces aggregation in muscle, improving motor performance, decreasing weight loss, and extending lifespan.

One of the first studies performed *in vivo* showing a protective effect of IGF-I in HD dates back to 1999 [239]. Daily administration of the natural cleavage product of IGF-I, GPE (the tripeptide Glycine-Proline-Glutamate) to a pharmacological model of HD almost fully restored the projection neurons of the striatum and the cholinergic and NADPHd-positive interneurons. Intranasal delivery of recombinant human IGF-I to the CNS elevated IGF-I cortical levels and Akt activity, increased phosphorylation of polyQ-HTT at serine 421, and it correlated with improvement of motor function as well as peripheral and central metabolic defects in YAC128 mice [240]. Based on the observations that IGF-I plasma levels are downregulated in HD mice, Duarte and

collaborators studied the effect of a continuous perfusion of recombinant IGF-I in HD mice [241]. Treatment significantly increased the plasma levels of IGF-I and ameliorated body weight loss and paw clasping, but it had no major effects on motor dysfunction. Naia and co-workers assessed the role of IGF-I versus insulin signaling, together with metabolism and mitochondrial functions in lymphoblast cells from HD patients [242]. IGF-I restored IGF-I and insulin downstream pathways (Akt and ERK) more potently than insulin, even if both neurotrophic factors phosphorylated polyQ-HTT at serine 421. IGF-I and insulin rescued energy levels in HD lymphoblasts, but only IGF-I ameliorated oxygen consumption and mitochondrial membrane potential. The same group analyzed the effect of insulin and IGF-I on mitochondrial function in primary striatal cells generated from HD knock-in mice, and showed that both trophic factors improve the mitochondrial function and reduce mitochondrial reactive oxygen species by activating the PI3K/Akt pathway [243]. Finally, they analyzed the energetic dysfunction after insulin and IGF-I treatment in striatal cells derived from HD knock-in mice. Striatal cells have decreased levels of ATP/ADP ratio and pyruvate dehydrogenase, and increased phosphocreatine and pyruvate levels. Both insulin and IGF-I restored phosphocreatine levels, whereas only IGF-I decreased pyruvate levels. The reduction in ATP/ADP and phosphocreatine levels were rescued after exposure to insulin or IGF-I [244]. The effect of IGF-I in different HD models seems to be protective, suggesting therapeutic potential for IGF-I also in this fatal polyQ disease.

### 3.4.3. Clinical trials of IGF-I

The pre-clinical studies described above led to evaluation of the clinical applicability of IGF-I. Treatment of 19 patients with type II/III SMA with GH did not improve muscle strength and function, indicating that the potential therapeutic strategies for SMA patients involving the use of GH to increase the release of IGF-I from the liver requires further investigation [245]. A double-blind, placebo-controlled, randomized clinical trial with recombinant IGF-I showed a mild decrease of functional impairment in ALS patients as compared to placebo-treated patients [246]. However, these results were not reproduced in a similar clinical trial carried out later on [247]. A combined meta-analysis of both trials showed slight retardation of the disease progression in the group treated with IGF-I, although the results were inconclusive [248]. A third trial showed modest, but significant protective effects of IGF-I [222]. Another trial completed in 2008 gave negative results [249]. The positive results obtained in animal

models of ALS and the negative outcomes obtained in clinical trials can be explained considering several factors, such as the use of SOD1-linked ALS mice, which may not recapitulate the complex genetics of sALS. In addition, the time of administration after symptom onset is a critical factor. Trophic factors have a short time frame for protection of motor neurons once the noxious process is triggered, which is probably due to the rate at which motor neurons die during the time course of the disease. In ALS mice the administration of IGF-I before the beginning of symptoms confers a significantly better protection, observed by a delay in the progression of symptoms and increased life span, as compared to that produced when treatment is administered at the symptom's onset. Another important factor is the IGF-I isoform used and its availability. A muscle-specific IGF-I isoform showed remarkable protective effects in mice when upregulated in skeletal muscles, yet this approach may have limitations in clinical practice. Nonetheless, IGF-I may have potential therapeutic effects in ALS that deserve further investigations in the novel mouse models of ALS recapitulating TDP43 pathology and C9ORF72 pathogenesis.

IGF-I-based therapies could be a valuable strategy for SBMA, because in addition to the benefits IGF-I confers on muscle and nerve survival, it also directly modifies polyQ-AR. Based on this premise, a clinical trial has been conducted testing BVS857, an IGF-I mimetic, in patients with SBMA. The recently published results show an increase in muscle volume without differences in muscle strength or function after 12 weeks of intravenous treatment with BVS857 [250]. The concern remains whether 12 weeks of treatment are sufficient to reverse the chronic toxicity of polyQ-AR. Finally, an *in vitro* electrophysiology study using a motor neuron model of SBMA, the MN100Q, shows a decrease in the current flow, mainly through potassium and calcium channel in the SBMA cells treated with testosterone. The treatment of the cells with IGF-I rescues the reduction of current flow, indicating that modulation of voltage-gated ionic currents is an additional target for IGF-I therapy in SBMA [251].

A prospective open label clinical trial in SCA3 and SCA7 patients with recombinant human IGF-I treatment showed improvement of some aspects of disease manifestations and progression, further extending the number of neurodegenerative diseases in which IGF-I seems to have beneficial effects [252].

**Conclusions**

Several lines of evidence suggest that IGF-I signaling is altered in neurodegenerative diseases. Critically, activation of such pathway has been shown to exert protective effects in different animal and cellular models of diseases of the CNS, implying that this approach may have therapeutic potential. However, translation to clinic has so far not been successful. This may be attributed to the fact that animals are often treated before or at disease onset, whereas patients are treated years after the estimated disease onset. Therefore, more evidence is needed to support the therapeutic potentials of IGF-I in humans. Nonetheless, IGF-I has remarkable anabolic, hypertrophic and anti-apoptotic effects in several tissues, which makes this molecule a unique potential disease modifier.

**Acknowledgments**

**Conflict of interests**

The authors have no conflict of interest to declare.

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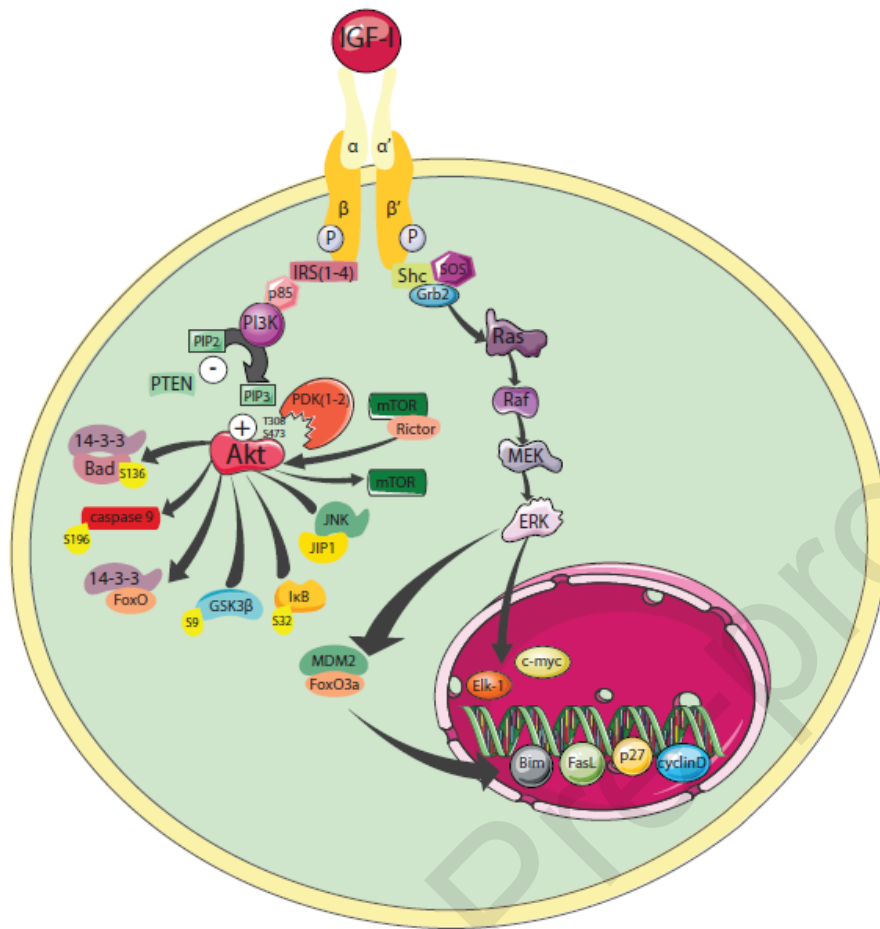
**Figure 1**



Figure 1. IGF-I signals through PI3K/Akt and Ras/ERK pathways. Schematic representation of the principal components of the intracellular pathways triggered upon binding of IGF-I to its receptors.
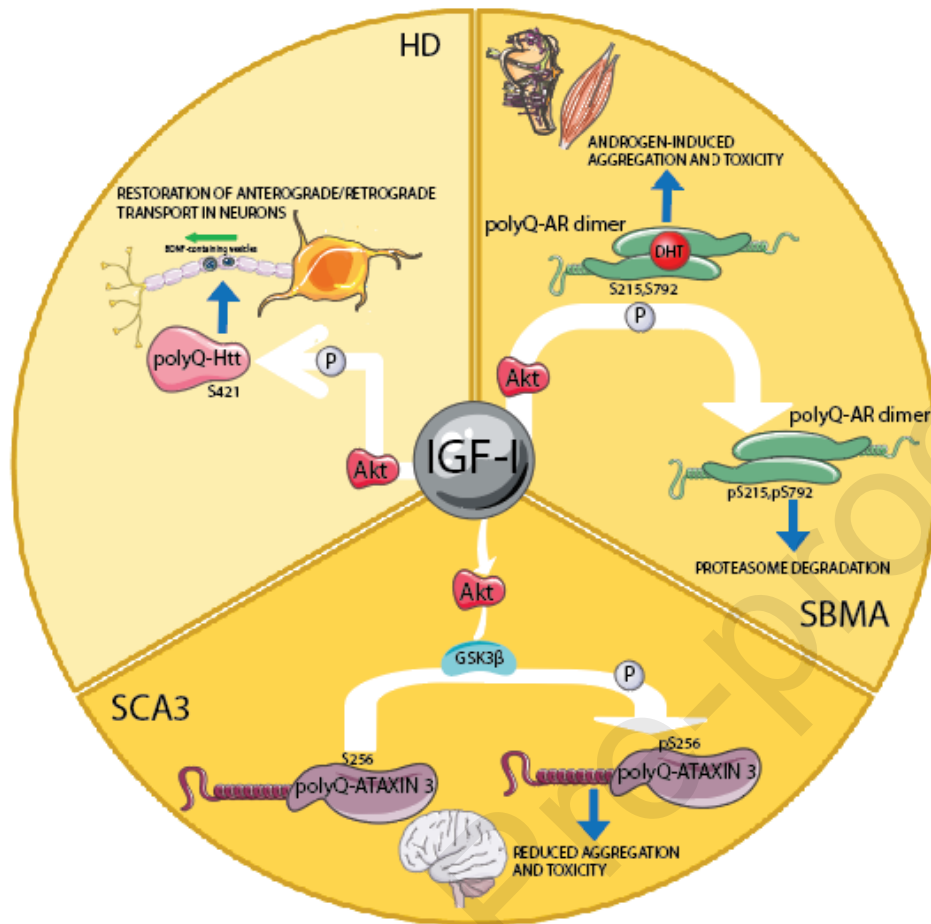
**Figure 2**



Figure 2. Direct modification of polyQ proteins by IGF-I signaling. The activation of Akt by IGF-I induces the phosphorylation of polyQ-AR, polyQ-ataxin-3, and polyQ-HTT, with major consequences on disease outcome.

Highlights

- IGF-I signaling in the physiology of nervous system and skeletal muscle
- Altered IGF-I signaling in neurodegeneration
- Aberrant post-translational modification of neurodegenerative disorders-related proteins
- Therapeutic perspectives of IGF-I for neurodegenerative diseases