The Role of Igf-1 on Muscle Wasting: a Therapeutic Approach

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Abstract

While much has been learned about skeletal muscle formation in the embryo, less is known about the molecular pathways controlling skeletal myocyte survival and plasticity in the adult. Tissue remodelling is an important physiological process which allows skeletal muscle to respond to environmental demands. In particular, the complex contractile properties of skeletal muscle depend upon a heterogeneous population of myofibers that confer the functional plasticity necessary to modulate responses to a wide range of external factors, including physical activity, change in hormone levels and motor-neuron activity, oxygen and nutrients supply. Fiber type is an essential determinant of muscle function and alteration in fiber composition represents a major component in muscle wasting associated with muscle diseases. In this context, the prolongation of skeletal muscle strength in aging and neuromuscular disease has been the objective of numerous studies employing a variety of approaches. To date however, efforts to prevent or attenuate age- or disease-related muscle degeneration have been largely unsuccessful. In this context, where direct therapeutic approaches to redress the primary disease are still sub-optimal, it may be more effective to focus on strategies for improving skeletal muscle function. In this review we will discuss the potential therapeutic role of Insulin-like Growth Factor 1 (IGF-1) in treatment of muscle wasting associated with several muscle diseases.

Key Words: muscle diseases, transgenic mice, growth factor, muscle regeneration, gene therapy.

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Molecular basis of muscle wasting

Although the genetic defects responsible for muscle dysfunction in several inherited pathologies have been well characterised, the molecular basis of muscle wasting remains elusive. It is generally accepted that the primary cause of functional impairment in muscle is a cumulative failure to repair damage related to an overall decrease in anabolic processes.

In the last decade, dramatic progress has been made in elucidating the molecular defects underlying a number of muscle diseases. However, the complexity of muscle types, the intimate relationship between structural integrity and mechanical function, and the sensitivity of skeletal muscle to metabolic perturbations have impeded rapid progress in successful clinical intervention. In addition, the relatively poor regenerative properties of striated muscle compound the devastating effects of muscle degeneration.

The skeletal musculature is particularly susceptible to the effects of aging and muscle diseases, undergoing a steady reduction in function and losing up to a third of its mass and strength. This decline in functional performance is due to an overall decrease in muscle integrity as fibrotic invasions replace functional contractile tissue, and marked changes occur in muscle fiber composition, with a characteristic loss in the fastest most powerful fibers. In fact, the age-related decrease in muscle mass involves a selective loss of fast glycolytic fibers (Type IIb) over fast oxidative fibers (Type IIa and Type IIx) or slow fibers (Type I) [1]. It is likely that as Type IIb fibers are lost, the muscles are forced to increasingly use Type IIa, Type IIx and Type I fibers to support movements. Although the remaining fibers are energetically more efficient than Type IIb

fibers, so that senescent muscle should become progressively more resistant to fatigue, they are also greatly decreased in their force-generating capacity, exhibiting restricted contractile options in terms of speed and power output.

The postmitotic nature of skeletal muscle tissue also limits its ability to effect repair or to regenerate. Muscle regeneration is a coordinate process in which several factors are sequentially activated to maintain and preserve muscle structure and function upon injured stimuli.

Although adult skeletal muscle is composed of fully differentiated fibers, it retains the capacity to regenerate in response to injury and to modify its contractile and metabolic properties in response to changing demand [6].

Regeneration is therefore an important homeostatic process, which guarantees the maintenance of muscle integrity and plasticity.

However, muscle regeneration results impaired in several muscle diseases.

The major role in the growth, remodelling and regeneration is played by satellite cells, a quiescent population of myogenic cells that reside between the basal lamina and plasmalemma [20]. Satellite cells are rapidly activated in response to appropriate stimuli; nevertheless, their number decreases substantially during the aging process and in neuromuscular diseases [28].

Role of IGF-1 on muscle differentiation

IGF-1 has been implicated in many anabolic pathways in skeletal muscle and it plays a central role during muscle regeneration [15, 19, 26]. Unlike other growth factors IGF-1 also stimulates myogenic differentiation and generates a pronounced hypertrophy of the muscle cells in vivo and in vitro [14, 16, 24, 27], suggesting that this growth factor can regulate both proliferative and differentiative responses in muscle cells. The effects of IGF-1 on proliferation and differentiation are temporally separated [11, 14, 18]. IGF-1 plays its roles step by step, first acting upon myoblast replication [14, 27] and subsequently promoting myogenic differentiation. Several experimental evidences suggest that IGF-1 exerts its functions by activating two different intracellular signal transduction pathways, conveying proliferative and differentiative signals, respectively. The proliferative response is mediated by the MAP-kinase pathway [11], whereas the pathway leading to differentiation involves the activation of PI3-Kinase [11, 18].

Exploitation of genetic and pharmacological manipulations has established a conclusive link between IGF-1 and calcineurin action [22, 29]. Calcineurin is a serine/threonine phosphatase activated by Ca2+/calmodulin, it is responsible for transducing environmental signals that control gene expression in several biological processes [12, 13] and has been recently implicated in hypertrophic cardiomyopathies [21], skeletal muscle differentiation [17] and specification of slow muscle phenotype [10]. Hypertrophic myocytes over-expressing IGF-1 activates calcineurin-mediated NFATc1 dephosphorylation and induction of GATA-2, a novel molecular marker of skeletal muscle hypertrophy [22].

Notably, activated calcineurin is able to promote myocycte hypertrophy in vitro [22] but not in vivo [25]. Rather, over expression of activated calcineurin transgene is sufficient to induce the slow fiber gene regulatory program [10, 25]. These data suggest that additional signals are required in vivo to support sustained skeletal muscle hypertrophy [5]. Alternatively, specific calcineurin isoforms may be necessary for the induction of the hypertrophic skeletal muscle phenotype in vivo.

Role of IGF-1 on muscle homeostasis

IGF-1 plays a key role in muscle development in vivo, and autocrine secretion of IGF-1 also facilitates muscle regeneration after injury [30] and in denervated muscle [7-9], suggesting that it acts as a muscle-derived neurotrophic factor.

To test the possibility that enhanced IGF-1 expression could affect a similar muscle hypertrophic response in muscle tissue in vivo, we recently generated a transgenic mouse in which the local isoform of IGF-1 (mIGF-1) is driven by MLC promoter (MLC/mIGF-1), thus specifically restricted to skeletal muscle tissue. Transgenic mice exhibit marked skeletal muscle hypertrophy with dramatic reduction in body fat and no undesirable side effects such as tumor formation, as revealed in transgenic mice over-expressing the circulating IGF-1 isoform [23].

Increased muscle mass in MLC/mIGF-1 transgenic muscle is associated with increased force generation compared to age-matched wild type littermates. Examination of older mice revealed that expression of the mIGF-1 transgene was protective against normal loss of muscle mass during senescence. Moreover mIGF-1 expression promotes and preserves the regeneration capacity of muscle tissues during aging, suggesting that IGF-1 expression preserves muscle integrity and the heterogeneity of myofibers, two fundamental parameters of muscle function. More recently we demonstrated that muscle-specific expression of mIGF-1 counters muscle wasting in mdx mouse which represent the animal model of human Duchenne and Becker muscular dystrophy. High levels of mIGF-1 transgene expression in the mdx mouse preserves muscle function in the absence of dystrophin, inducing significant hypertrophy and hyperplasia at all ages observed, reducing fibrosis and myonecrosis, and elevating signaling pathways associated with muscle survival and regeneration [2].

These results demonstrated that expression of the mIGF-1 transgene safely enhanced and preserved

muscle fiber integrity even at advanced ages and in the dystrophic muscle, suggesting that the MLC/mIGF-1 transgene acts as a survival factor by prolonging the regenerative potential of senescent muscle.

IGF-1 and therapeutic strategies

There is considerable clinical interest in therapeutic strategies that sustain muscle regeneration and repair for treatment of muscle wasting conditions, such as aging, muscular dystrophies, trauma, and injuries.

The studies discussed in this review support a role for IGF-1 in the establishment and maintenance of the mature muscle phenotype in normal and cultured muscle tissue and suggest that IGF-1 represents a good candidate to sustain muscle hypertrophy and to improve muscle regeneration.

Gene therapy represents a promising tool to cure, when it is possible, or attenuate the genetic diseases leading to muscle wasting. Gene therapy relies on either viral or non-viral vectors to delivery target genes into somatic adult cells. Non viral-vectors present several limitations due to the instability of such system cells.

In order to be effective, gene therapy must satisfy four major parameters: the vectors has to be able to carry the target gene, has to be cheaply produced in large quantity, has to produce low immune-response and has to be stable expressed.

Using such approaches we determined that the capacity of the mIGF-1 transgene to attenuate the structural and functional consequences of muscle aging was independent of its action during embryogenesis or early postnatal life.

Introduction of mIGF-1 somatically using an Adeno-Associated-Viral (AAV) vector was sufficient to rejuvenate the leg muscles of 27 month old mice, which exhibited the same mechanical force as legs of younger mice, and did not develop the pathological characteristics of senescent muscle [3]. The dramatic hypertrophy induced by expression of virally delivered IGF-1 is the consequence of a combination of satellite cell activation and an increase of protein synthesis [3, 4]. In addition, age-related reduction in force production and loss of fast fibers, all of which are typical of ageing skeletal muscle, were prevented both by virally delivered IGF-1 gene expression [3].

Understanding the signal transduction pathways involved in muscle wasting will help to devise therapeutic strategies to combat muscle degeneration. Blocking proteolytic pathways or inducing muscle regeneration with pharmacological intervention will require a detailed knowledge of the signalling mechanisms involved, and the extent to which blocking or enhancing these pathways will be detrimental to other physiological parameters such as motor innervation.

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