

INDUCING MUSCLE HYPERTROPHY AS A THERAPEUTIC STRATEGY FOR MUSCLE WASTING: ROLE OF IGF-1

Antonio Musarò, Cristina Giacinti, Gabriella Dobrowolny, Laura Pelosi, Laura Barberi, Mario Molinaro

Department of Histology and Medical Embryology; University of Rome La Sapienza.

Abstract

The prolongation of skeletal muscle strength in aging and neuromuscular disease has been the objective of numerous studies employing a variety of approaches.

The characteristic loss in muscle mass, coupled with a decrease in strength and force output, has been associated with a selective activation of apoptotic pathways and a general reduction in survival mechanisms. Aging and genetic diseases, such as muscular dystrophies, amyotrophic lateral sclerosis, cancer and AIDS, are characterized by alterations in metabolic and physiological parameters, progressive weakness in specific muscle groups, modulation in muscle-specific transcriptional mechanisms and persistent protein degradation.

Although considerable information has accumulated regarding the physiopathology of muscle diseases, the associated molecular mechanisms are still poorly understood.

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.

Text

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 remodeling 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 [1]. Fiber type is an essential determinant of muscle function and alteration in fiber composition represents a major component in the muscle degeneration associated with muscle diseases.

Chronic protein degradation is one of the most devastating consequences of defects in muscle survival mechanisms. For example, one of the most severe characteristics of muscular dystrophy is the progressive loss of muscle tissue due to chronic degeneration of muscle and to the exhaustion of satellite cells that replace damaged fibers [2].

Thus, the persistent protein degradation observed in neuromuscular diseases reflects a pathological muscle catabolism.

To date however, efforts to prevent or attenuate age- or disease-related muscle degeneration have been largely unsuccessful. Cell-based therapies have been stalled by the difficulty in obtaining sufficient numbers of autologous myoblasts and by inefficient incorporation into host muscle [3,4].

The identification of multi-potent stem cells residing in extra-hematopoietic adult tissues has offered new perspectives in cell-mediated therapy for genetic diseases. Small numbers of haematopoietic stem cells (HSC) reside in the muscle beds of non-injured animals and more migrate into sites of injury, suggesting a mechanism by which damaged tissues are repaired [5]. However this seems a rare event and presents limitations for an efficient tissue repair.

Administration of growth hormone prevents age-related loss of muscle mass, but has failed to increase muscle strength.

Experimental models of muscle growth and regeneration have implicated Insulin-like Growth Factor-1 (IGF-1) as an important mediator of anabolic pathways in skeletal muscle cells [6]. In particular, IGF-1 is a key factor in the induction of muscle hypertrophy, thus a potential therapeutic approach that could counteract muscle atrophy observed in aged and pathological muscle is the induction of an increase in muscle mass.

We have generated a transgenic mouse carrying a local isoform of IGF-1 (mIGF-1) under the control of the muscle-specific regulatory elements from the MLC1/3 locus [7]. These mice display increased muscle mass associated with increased force generation compared to age-matched wild type littermates. Examination of older mice revealed that expression of the mIGF-1 transgene is protective against normal loss of muscle mass, promoting muscle regeneration [7].

In addition, high levels of mIGF-1 transgene expression in the mdx mouse model of muscular dystrophy also 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 [8].

In addition, we analyzed whether muscle regeneration involved the recruitment of uncommitted cell populations. We demonstrated that the capacity of the transgenic muscle to regenerate is also associated to an increase in the recruitment of circulating stem cells expressing Scd1, CD45 and c-Kit, general markers of hematopoietic stem cells [9]. The recruited uncommitted cells homing the damage muscle, contribute to muscle regeneration and guarantee a reserve of muscle stem cells.

IGF-1 can therefore act, in combination with other regenerative factors, as a homing signal attracting circulating stem cells to repair injured muscle.

All of these evidences suggest that IGF1 activates regenerative processes and survival pathways leading to maintenance of muscle phenotype and attenuation of muscle atrophy and disease.

Reference

- [1] Buonanno A., Rosenthal N.: Molecular control of muscle diversity and plasticity. *Dev. Genet.* 1996, 19:95-107.
- [2] Musarò A, Rosenthal N. Attenuating muscle wasting: cell and gene therapy approaches. *Current Genomics* 2003; 4:575-585.
- [3] Grounds, M.D. Myoblast transfer therapy in the new millennium. *Cell Transplant.*, 2000, 9: 485-487.
- [4] Grounds, M.D., White, J.D., Rosenthal, N., Bogoyevitch, M.A. The role of stem cells in skeletal and cardiac muscle repair. *J. Histochem. Cytochem.*, 2002, 50: 589-610.
- [5] Blau, H.M., Brazelton, T.R., Weimann, J.M. The evolving concept of a stem cell: entity or function? *Cell*, 2001, 105: 829-841.
- [6] Musarò A., Rosenthal N: The role of local Insulin-like Growth Factor-1 isoforms in the pathophysiology of skeletal muscle. *Current Genomics* 2002; 3: 149-162.
- [7] Musarò A, Mc Cullagh K, Paul A, Houghton L, Dobrowolny G, Molinaro M., Barton ER, Sweeney LH, Rosenthal N: Localized Igf-1 transgene expression sustains hypertrophy and regeneration in senescent skeletal muscle. *Nature Genetics* 2001; 27: 195-200.
- [8] Barton ER, Morris L, Musarò A, Rosenthal N, Sweeney HL: Muscle-specific expression of insulin-like growth factor I counters muscle decline in mdx mice. *J Cell Biol.* 2002; 157: 137-48.
- [9] Musarò A, Giacinti C, Borsellino G, Dobrowolny G, Pelosi L, Cairns L, Ottolenghi S, Bernardi G, Cossu G, Battistini L, Molinaro M, Rosenthal N. Muscle restricted expression of mIGF-1 enhances the recruitment of stem cells during muscle regeneration. *PNAS* 2004; 101: 1206-1210.

Author's address:

Dr. Antonio Musarò
Department of Histology and Medical Embryology;
Interuniversity Institute of Myology, University of Rome La
Sapienza, Via A. Scarpa, 14 00161 Rome
e-mail: antonio.musaro@uniroma1.it