J Musculoskelet Neuronal Interact 2007; 7(3):246-252

Review Article

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Age-related skeletal muscle dysfunction: causes and mechanisms

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Abstract

Age-related muscle weakening may ultimately result in the transition from an independent to a dependent life-style. The decline in muscle strength is larger than expected from the loss of muscle mass. Single fibre studies and *in vitro* motility assays indicate that part of the muscle dysfunction is due to modifications of the myosin molecule. A lower rate of protein turnover may increase the chance of post-translational modifications such as oxidation and glycation. The impaired regenerative capacity of old muscles is related to a lower differentiation capacity of myosatellite cells, which is most likely due to altered transcriptional activity of myogenic regulatory factors (MRFs). However, old myosatellite cells can be rejuvenated when exposed to serum from young individuals. This indicates that alterations in the environment of the satellite cells or circulating substances play an important role in impaired differentiation capacity of satellite cells in old age. It is proposed that systemic inflammation may be that factor. Indeed, the inflammatory cytokine tumour necrosis factor-α: 1) impairs transcriptional regulation by MRFs, 2) suppresses myosatellite cell differentiation and 3) induces apoptosis. Moreover, muscle mass, strength and the response to strength training in old age are all inversely related to the degree of systemic inflammation.

Keywords: Specific Tension, Shortening Velocity, Ageing, Systemic Inflammation, Myogenic Regulatory Factors, Apoptosis

Introduction

The proportion of elderly people in the Western World is increasing steadily. The result of the ageing process is a decline in organ function and skeletal muscle is no exception to this. Indeed, the progressive loss of muscle mass contributes significantly to the decline in the quality of life during ageing. Ultimately, the loss of mobility that accompanies muscle wasting may cause the transition from an independent to a dependent life-style, particularly when the rate of muscle wasting is accelerated such as during hospitalisation. Besides impaired balance due to muscle weakness[1], slowing of the muscle may limit the ability to prevent falls thus contributing to the increased incidence of fall-related injuries in old age[2]. Finally, loss of muscle strength appears to be a strong predictor of the risk of mortality[3]. Clearly, a thorough understanding of the causes and mechanisms of muscle wasting and dysfunction that occurs with ageing is indispensable to develop strategies aimed at attenuating or reversing the age-related decline in muscle mass and function.

Causes of muscle wasting during ageing

Neural degeneration

Ageing is associated with a progressive loss of motor neurons and, as a consequence, muscle fibres become denervated. Fortunately, many fibres are re-innervated by other motor neurons thereby minimising the loss of functional muscle fibres. However, the process is insufficient to fully compensate for denervation resulting in atrophy and progressive loss of muscle fibres[4]. Fast motor neurons seem to be preferentially affected and over time the denervation/re-innervation process may result in loss and atrophy of type II fibres and fibre type grouping of particularly type I fibres[4,5].

Vascular endothelial growth factor (VEGF) has been shown to attenuate the loss of motor neurons in mice models

The author has no conflict of interest.

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Accepted 30 January 2007

of amyotrophic lateral sclerosis and other neurodegenerative disorders[6]. It is possible that an attenuated VEGF response to ischaemia in old age, as observed in rabbit muscle tissue[7], and/or an inadequate perfusion of the spinal cord may underlie the loss of motor neurons seen with increasing age.

Disuse

The level of physical activity steadily declines with age[8,9] and disuse contributes to the decline in muscle mass and function[10]. However, where disuse as a result of, for instance, immobilisation is accompanied by a slow-to-fast transition in fibre type composition, ageing is accompanied by a fast-to-slow transition[10]. This fast-to-slow transition is at least partly a consequence of the denervation and re-innervation process. In addition, highly active elderly people, such as master swimmers and athletes, still have lower muscle mass and strength than young controls and only resistance trained master athletes have a similar strength and muscle size as sedentary young controls[11]. Even in sprint-trained master athletes the age-related slowing and decline in specific tension of type I and IIa fibres was not reversed[12,13]. It thus appears that factors other than disuse contribute to the muscle wasting and dysfunction during ageing.

Age-related muscle weakness and slowing

Ageing is not only associated with muscle weakening[1,9-11,14-17], but also by a slowing of the muscle[11,15,16,18] and consequently a loss of power generating capacity[19-21]. Several factors contribute to this decline in muscle function, with the obvious one being a loss of muscle mass[11,16,17]. The decline in muscle mass, a combination of a loss of fibres[5] and preferential type II fibre atrophy[5,11] does, however, not entirely explain muscle dysfunction during ageing. Indeed, muscle weakness is more pronounced than muscle atrophy, as reflected by a decrease in force per anatomical cross-sectional area[11,17,18]. Several factors may explain this decline in force per anatomical cross-sectional area, such as alterations in fibre type composition, the extent of voluntary activation, co-activation of antagonists and/or altered muscle architecture.

It is unlikely that the shift from type II to type I fibres would significantly contribute to the age-related loss of isometric strength, as specific tension (force per physiological cross-sectional area) does not differ significantly between different fibre types[22,23]. The ability to voluntarily activate a muscle has been reported to be reduced but co-activation of antagonistic muscles was similar in young and old people[17]. During ageing, a change in muscle architecture may further explain the decline in strength. Yet, the decrease in specific tension, calculated from muscle volume, fascicle length and pennation angle, was more marked than the decline in force per anatomical cross-sectional area[17] indicating that at least in the gastrocnemius muscle, changes in muscle architecture do not explain muscle weakness in old age. Although it is possible that an increase in connective and adipose tissue content could cause a reduction in force generated per cross-sectional area of muscle, this did not explain the age-related decline in specific tension in the rat plantaris muscle[24]. Finally, an increase in tendon compliance in old age[1] may cause a shortening of the sarcomeres during a contraction to such an extent that the muscle functions at a sub-optimal length causing a loss of force generating capacity[18]. However, taking into account all the above mentioned factors still does not entirely explain the age-related muscle weakening, suggesting some alterations within the muscle fibres themselves. Indeed, a decrease in specific tension is a common observation in single skinned muscle fibres[13,25-27].

The age-related slowing is to some extent due to a reduction in fascicle length and increased tendon compliance[18]. Since the shortening velocity of type II fibres is considerably higher than that of type I fibres[22,28,29], a more substantial cause for the slowing is the preferential loss of type II fibres, causing an increase in the proportion of the muscle cross-sectional area occupied by type I fibres[11]. Yet, even at the level of the single fibre, type I and IIa fibres exhibit an age-related slowing, as reflected in a reduced unloaded shortening velocity, independent of any change in myosin heavy or light chain composition[13,25,30,31]. This suggests that alterations in the myosin and/or actin filament take place during ageing.

Alterations in the myosin molecule

As indicated above, the declines in specific tension and shortening velocity of single permeabilised muscle fibres of a given type suggest that during ageing structural alterations in the actin and or myosin filament take place. With *in vitro* motility assays a similar decline in the velocity of movement of actin filaments over slides coated with myosin isolated from single rat fibres indicated that the myosin molecule has indeed undergone some changes during ageing[32]. Evidence has been obtained that an increased oxidation of myosin by free radicals contributes to a decreased fraction of strongly attached cross-bridges, which almost entirely explains the age-related decline in specific tension of single rat skinned muscle fibres[26,27]. Another factor that may play a role in the muscle dysfunction of old age is the increase in glycated myosin[33] as a consequence of a decrease in insulin sensitivity and poor control of circulating glucose with advancing years. *In vitro* motility assays reveal that incubation of myosin with glucose, giving rise to glycation of the myosin molecule, resulted in a marked decrease in the velocity of the actin filaments, which was completely reversible by deglycation with glutathione[34,35].

Muscle degeneration and regeneration

Oxidative stress and protein turnover

When one considers that post-translational modification of myosin, such as by oxidation or glycation, affects muscle function the question arises as to the cause of these modifications.

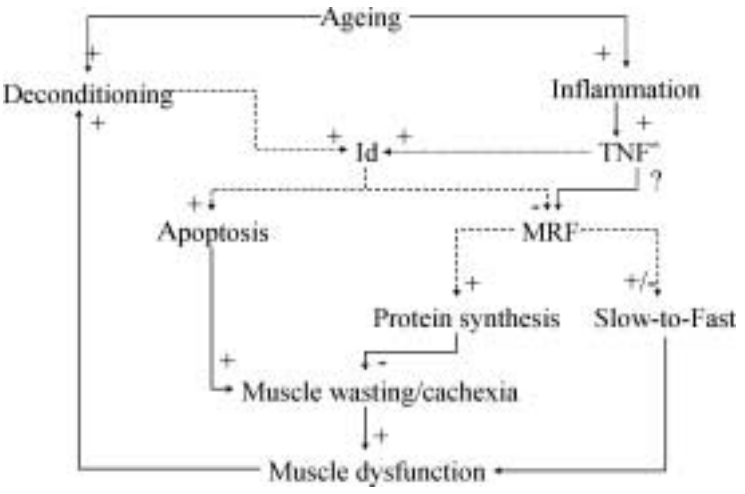

Figure 1. The role of myogenic regulatory factors (MRFs) and inhibitors of differentiation (Id) proteins on muscle wasting during ageing. TNF-α: tumour necrosis factor-α; solid lines indicate relations observed; broken lines indicate relations observed in cell culture and animal studies.

Clearly, oxidation of the myosin molecule must be a reflection of oxidative stress, and the 'free radical theory of ageing' suggests that the oxidative stress will increase with increasing age. This oxidative stress may be the result of an accumulation of 'minihits', such as exposure to pollutants and events of transient hypoxia which not only reduce the efficiency of mitochondria but also increase the formation of reactive oxygen species (ROS)[36]. Systemic inflammation, and in particular circulating levels of Tumour Necrosis Factor-α (TNFα), may increase the rate at which ROS are made[37]. Furthermore, the damaging effect of ROS may be elevated in old age due to a reduced ability to induce Heat Shock Protein 70 (HSP70), a molecule which may protect against damage caused by ROS. In line with this, it was found that muscles from old mice over-expressing HSP70 recovered better from damage than normal old mice[38,39]. Another possibility is that the replacement of muscle proteins, including myosin, is delayed with ageing, thereby increasing the chance of post-translational modification. If this is the case this should be reflected by a decreased rate of protein turnover during ageing. Indeed, the synthesis rate of myosin is reduced with age[40], and the activity of the ubiquitin proteasome pathway, a complex that plays an important role in protein degradation during muscle atrophy, has been reported to be reduced in rat skeletal muscle[41]. Myogenic regulatory factors (MRFs) play an important role in the transcription of muscle specific genes, and hence the synthesis of muscle specific proteins. Hence, the role of these proteins, and inhibitor of differentiation (Id) proteins, in muscle regeneration and wasting will be discussed in more detail (Figure 1).

Myogenic regulatory factors and inhibitors of differentiation

Myosatellite cells are central to muscle regeneration. Although the proliferative capacity of satellite cells is maintained during ageing, their number and capacity to differentiate is diminished[42-44]. During the regenerative process the satellite cells divide and subsequently differentiate, and the induction of MRFs is crucial for this process[44]. The MRF genes are a family of four muscle-specific transcription factors, myf-5, MyoD, myogenin and MRF4, regulating the expression of muscle specific genes during the various stages of differentiation of muscle tissue. They exert their role by dimerisation with E-proteins, allowing them to bind to E-boxes on DNA and initiating muscle specific gene transcription. It is thus possible that alterations in MRF expression or activity may play a role in muscle wasting during ageing (Figure 1).

Although the elevated mRNA levels of MRFs[8,45] and insulin-like growth factor-I (IGF-I) suggest that the regenerative drive is intact in old muscle, differentiation is impaired indicating that muscle wasting in ageing is at least partly related to a failure to differentiate[8]. At first glance this seems contradictory, as MRFs play an important role in satellite cell differentiation[44]. However, mRNA levels do not necessarily reflect protein levels of MRFs. Indeed, in rat skeletal muscle MRF protein levels have been reported to be reduced during ageing even in the presence of elevated mRNA levels[45]. In addition, the abundance of E-proteins, the obligatory dimerisation partners of MRFs, is decreased and may contribute to the reduced transcription of muscle specific genes under the control of MRFs[45]. Finally, increased expression of inhibitors of differentiation (Id) proteins, although they stimulate satellite cell proliferation[46], may inhibit their differentiation.

Although elevated expression of Id proteins in old age[45] may seem beneficial as they stimulate satellite cell proliferation, muscle fibres from transgenic mice over-expressing Id proteins are atrophied[47]. Id proteins may cause atrophy by

impairing the activity of MRFs in three ways. First, Id proteins dimerise with E-proteins and by sequestration of the E-proteins diminish E-protein/MRF dimerisation which is a pre-requisite for the transcriptional activity of the MRFs[48]. Secondly, Id proteins may form heterodimers with MRFs precluding the MRFs from binding to DNA[48]. Thirdly, heterodimerisation of MRFs with Id proteins makes the MRFs more vulnerable to breakdown via the ubiquitin proteasome pathway[49]. The elevated mRNA levels of MRFs in old age[45] may be a means to offset to some extent the loss of MRF activity[49]. Besides hampering the activity of the MRFs, Id proteins might also induce apoptosis[46,50]. Indeed, the elevated apoptosis seen in old age correlated positively with the expression of Id proteins[51]. Thus, elevated expression of Id proteins and reduced protein expression and hampered function of MRFs may underlie the impaired differentiation of satellite cells[44], diminished muscle protein synthesis and increased apoptosis in old age. A further indication that reduced expression of MRFs may play a role in skeletal muscle wasting and dysfunction is the observation that similar to ageing, bundles of the diaphragm of MyoD-/- mice produce a lower specific tension, are slower and consequently have a lower power generating capacity[52], possibly due to e.g., an altered expression of proteins under the control of MyoD such as desmin. A question that may arise is to what causes the altered expression of these proteins.

The cellular environment

The reduced regenerative capacity of the muscle seems reversible since old muscle when transplanted in a young animal regenerates as well as a young muscle transplanted in a young animal[53]. Muscle regeneration in old animals could be improved when they shared their circulatory system with young animals and satellite cells were rejuvenated when exposed to serum of young mice[42]. Conversely, transplantation of a young muscle into an old animal[53] and exposure of satellite cells from young animals to serum from old animals[42] attenuated their regenerative capacity. These observations strongly hint at age-related changes in circulating substances affecting the regenerative potential of the ageing satellite cell. This is a promising observation as it may open avenues to increase muscle mass and improve function also in old age.

One of the changes in circulating substances is a reduced level of anabolic hormones, such as IGF-I and testosterone[40] which decrease with age. The anabolic effect of these hormones may be limited by elevated systemic inflammatory cytokines such as TNFα and IL-6. For instance, there is a lack of correlation between strength and circulating IGF-I in elderly people when IL-6 levels are high[19]. Moreover, TNFα levels in the blood and muscle tissue are negatively related to muscle mass and strength in the elderly[54-56] and in many disorders, such as chronic obstructive pulmonary disease and heart failure, the muscle wasting is often associated with elevated levels of plasma TNFα[57,58]. In rats, attenuation of the age-related muscle fibre atrophy was achieved with life-long caloric restriction which was associated with a diminished rise in plasma TNFα levels[59]. Finally, exposure of myoblasts to TNFα induces apoptosis and suppresses differentiation[60]. Therefore, it is proposed that an elevated level of inflammatory cytokines, and in particular TNFα, is the main change in circulating substances that contributes to muscle wasting during ageing.

The effects of TNFα may be partly mediated by its effect on MRF and Id protein expression. The expression of MyoD and myogenin was reduced in myoblasts exposed to TNFα, resulting in reduced mRNA levels of myosin and myofilament synthesis[61]. Also in mice treated with TNFα muscle regeneration was impaired as a result of the destabilisation of MyoD[62]. It is therefore tempting to speculate that the inverse relation of muscle protein synthesis rate and TNFα levels in the muscle of elderly people[55] is at least partly mediated by the effect of TNFα on MRF expression.

As TNFα modulates the expression of Id proteins in neural tissue[63], it is possible that the age-related increase in apoptosis in skeletal muscle is, besides the induction of apoptosis via the death domain[59,64], at least partly mediated by an increased expression of Id proteins induced by TNFα.

Response to exercise

Skeletal muscle is a highly adaptive tissue and responds readily to altered functional demands. Where endurance training and chronic electrical stimulation cause an increase in the oxidative capacity and strength training or overload lead to hypertrophy, disuse is accompanied by muscle atrophy[10,65]. Even in old age resistance training has been shown to increase muscle mass and strength[18,66] and an increase in tendon stiffness results in a more rapid rise of force during a contraction[18]. Furthermore, also in old age training reduces the expression of TNFα[55] and occurrence of apoptosis[67], and may even protect against apoptosis during periods of increased disuse as would occur during hospitalisation[64]. This suggests that training provides an excellent means to improve muscle function.

There is evidence, however, that muscle plasticity may decrease with age, as reflected by attenuated hypertrophy[10,14,68,69], which may even be accompanied by muscle weakening rather than an increase in strength[10,14], and a delayed and incomplete adaptation to chronic electrical stimulation[70]. Part of this impaired response in old age may be brought about by an attenuated activation of the mTOR pathway following a single bout of exercise[71] and a diminished ability of satellite cells to differentiate[44]. In particular the frail elderly fail to respond positively. In those people the response is inversely related to the level of TNFα, or soluble TNF-receptor, in the blood/muscle[54,55]. This may be related to the ability of TNFα to induce its own expression via a positive feedback loop[72]. Indeed, in transgenic mice overexpressing TNFα in the lung, which also exhibit elevated TNFα levels in the blood and muscle tissue, the response to reload-

ing after a period of unloading was severely diminished, due to impaired proliferation and differentiation of satellite cells[72]. This suggests that the benefits of training are limited by, in particular, systemic inflammation.

Summary and conclusion

The age-related weakness and slowing of skeletal muscle is not only attributable to muscle wasting and changes in fibre type composition, but also to post-translational modifications of the myosin molecule. Part of this may be due to a lower rate of protein turnover increasing the chance of protein modifications. The impaired regenerative capacity of older muscle is related to a lower differentiation capacity of myosatellite cells, which is most likely due to altered transcriptional activity of myogenic regulatory factors. However, old myosatellite cells can be rejuvenated when exposed to serum from young individuals. This indicates that alterations in the environment of the satellite cells or circulating substances play an important role in the impaired differentiation capacity of satellite cells at old age. It is proposed that systemic inflammation may be that factor, as muscle mass, strength and the response to strength training in old age are all inversely related to the degree of systemic inflammation.

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