Available online at www.sciencedirect.com

Integrative Medicine Research

journal homepage: www.imr-journal.com

Review Article

Age-related functional changes and susceptibility to eccentric contraction-induced damage in skeletal muscle cell

*Seung-Jun Choi**

Division of Sports and Health Science, Kyungsung University, Busan, Korea

ARTICLE INFO

Article history:
Received 23 March 2016
Received in revised form
12 May 2016
Accepted 12 May 2016
Available online 20 May 2016

Keywords:
aging
eccentric contraction
fiber type heterogeneity
muscle damage

ABSTRACT

Depending upon external loading conditions, skeletal muscles can either shorten, lengthen, or remain at a fixed length as they produce force. Fixed-end or isometric contractions stabilize joints and allow muscles to act as active struts during locomotion. Active muscles dissipate energy when they are lengthened by an external force that exceeds their current force producing capacity. These unaccustomed eccentric activities often lead to muscle weakness, soreness, and inflammation. During aging, the ability to produce force under these conditions is reduced and appears to be due to not only reductions in muscle mass but also to alterations in the basic mechanisms of contraction. These alterations include impairments in the excitation–contraction process, and the action of the cross-bridges. Also, it is well known that age-related skeletal muscle atrophy is characterized by a preferential atrophy of fast fibers, and increased susceptibility to fast muscle fiber when aged muscles are exposed to eccentric contraction followed by the impaired recovery process has been reported. Taken together, the selective loss of fast muscle fiber in aged muscle could be affected by eccentric-induced muscle damage, which has significant implication to identify the etiology of the age-related functional changes. Therefore, in this review the alteration of age-related muscle function and its impact to/of eccentric induced muscle damage and recovery will be addressed in detail.

1. Introduction

Age-related sarcopenia is characterized by a loss of skeletal muscle mass and a gradual decline in the functional properties of the tissue.[1–4] Because of the clinical importance of these functional changes, and the demographic changes projected for the next 20 years, considerable attention has been focused on understanding how aging affects skeletal muscle contractility.

The ability to generate force under isometric or shortening conditions is reduced in old age and appears to be due to not only a selective atrophy or loss of fast contracting fiber types,[5–7] impairments in the excitation–contraction

* Division of Sports and Health Science, College of Art, Kyungsung University, 309 Suyeong-ro, Nam-Gu, Busan 48434, Republic of Korea.
E-mail address: choisj@ks.ac.kr

http://dx.doi.org/10.1016/j.imr.2016.05.004

(EC) coupling process,[8,9] and perturbations to cross-bridge function.[10–12] In addition to isometric or shortening contractions, muscle must also actively resist stretch by an external force. This ability to resist, but not prevent, lengthening allows muscles to function as brakes or shock absorbers. These lengthening, eccentric, or pliometric contractions occur frequently during everyday activities. Force production during eccentric contractions appears to be better preserved with age than strength during isometric or shortening contractions.[13,14] However, in young individuals, unaccustomed or excessive eccentric muscular activity can lead to long-lasting weakness, soreness, and inflammation[15–19] and these effects may be exacerbated with age.

Aged muscles are more sensitive to eccentric contraction, at least in animal models.[20–23] However, human studies examining the effect of eccentric-induced muscle damage on old adults have not reached a consensus. Several human studies have reported that older adults show an increased susceptibility to damage by a single bout of eccentric exercise performed by knee extensors compared to younger adults.[24,25] By contrast, others have reported that the loss of maximal isometric contraction was the same[26] or less for old adults *vs.* young adults following voluntary eccentric exercise by the elbow flexors.[27,28] These contradictory results of eccentric-induced muscle damage on aging may be due to the inability to adequately control important factors contributing to muscle damage, such as strain magnitude,[29] intramuscular fiber pennation, and motor unit recruitment patterns in human muscle. Furthermore, age group differences in muscle mass, fiber type composition, and mechanical stress may complicate experimental design and interpretation.

Few studies have examined the susceptibility of human muscle fibers after eccentric-contraction, especially in muscles experiencing sarcopenia. Furthermore, any preferential damage to fast twitch fibers could exacerbate the symptoms of sarcopenia. It is therefore critical to understand how different fiber types respond mechanically to eccentric-induced muscle injury, especially for aged populations. Therefore, the aim of this review is to explore details about the age-related functional changes particularly in skeletal muscle cell, and its relationship with eccentric-induced muscle damage and recovery.

2. Age-related functional changes in skeletal muscle

Sarcopenia is a general term to describe the gradual decline of muscle mass with aging. It is characterized by not only the loss of skeletal muscle mass, but also the gradual decline in muscle functional properties, such as a decline in force generating capacity, maximum shortening velocity, and a general slowing of contraction.[1–4] This age-related muscle atrophy is thought to be derived from a decrease in both muscle quantity (mass), and a decrease in muscle quality (force per cross-sectional area of muscle, proportion of fiber types and metabolic characteristics).[3]

The loss of muscle quantity appears to be mainly due to a degradation of contractile protein, resulting from both the reduction of number of single muscle fibers, and a decrease in the cross-sectional area (CSA) of residual muscle fibers. For example, the CSA of muscle decrease by up to 30%, and muscle strength by about 30–40% between the ages of 65 years and 75 years.[30] This age-related decline of contractile protein content could be explained by different rates of protein degradation and protein synthesis.[31] The main determinant of the loss of contractile protein content is protein degradation rather than protein synthesis.[32] Also type II fibers are primarily atrophied compared to the type I fibers.[6,7] The age-related decrease in muscle quality indicates that both the time taken to reach peak twitch tension and the time taken for the muscle twitch response to relax are increased in old muscle.[33] This could be due to several different mechanisms, including an increase in the level of intramuscular collagen and fat, a decline in specific force, an alteration of EC coupling,[34–36] neurogenic factors, or motor unit remodeling (denervation and reinnervation).

Even though it is generally accepted that the contractile properties of muscle are decreased with aging, the effects of aging on the intrinsic ability of single fibers are still equivocal. That is, the results of skinned single fiber studies on maximal isometric force (P_o), and unloaded shortening velocity between young and old humans are not consistent. Several studies have reported that there were significant reduction in the intrinsic contractile properties with aging, such as reductions in P_o, normalized force by CSA (P_o/CSA), and unloaded shortening velocity.[11,37–40] This suggests that both size and quality of each individual muscle fiber decrease with age. The proposed mechanisms to explain the declined intrinsic force generating ability of aged fibers are either a lower number of strongly bound cross-bridges during maximal activation or a reduced force-generating ability of each cross-bridge.[40] According to Lowe and colleagues,[12] when a muscle fiber contracts maximally, about 32% of myosin heads are in the strong-binding state. However, only 22% of myosin heads are in that state in fibers from older rats. Thus, the decreased P_o in the elderly may due to a decreased numbers of cross-bridges per CSA.[11] Also, there is a loss of myofibillar protein in old rats, which may lead to a reduction in the motor proteins actin and myosin.[10] Slowing of shortening velocity with aging is thought to involve a slowing of the steps within the cross-bridge cycle, such as the actin–myosin cross-bridge detachment rate.[39] It is proposed that this occurs without a change in isoform type,[41,42] and may be related to glycation of myosin.[43]

By contrast, more recent studies have found that contractile quality of single muscle fiber is maintained during aging[44–47] or increased in maximal force in both fiber types with aging.[48,49] In other words, there was no change of intrinsic ability of single fiber with aging among young and old men and women. This suggests that the intrinsic properties of cross-bridge mechanics are preserved with age.[47]

3. Age-related susceptibility to eccentric contraction induced muscle damage

Several studies have considered the different susceptibility of muscles from young and old to damage induced by eccentric contractions using both animal and human models. The general consensus of the animal studies is that an

increased susceptibility of aged muscle to eccentric contractions has been observed consistently in studies performed on isolated rodent muscles.[20–23] In detail, force deficits were two-fold greater after maximally activated single stretches in single fibers from old rodent extensor digitorum longus (EDL) muscles, compared with young.[50,51] After a single eccentric contraction (strains of 5%, 10%, 20%, or 30%), EDL fibers from old rats showed greater force deficit than fibers from young rats up to 20% strain. At 30% of strain, the force deficit was not different between age groups. A breakage rate was reported while fibers were stretched, and it was much greater for old fibers at all strains: about 22% higher at a 20% strain and 45% higher at a 30% strain. Also, the relationship between force deficit and amount of strain was investigated. It was revealed that the force deficit of old muscles had a different pattern compared with young muscle. The young muscles tend to have a linear increase in the force deficit as the strain increased from 20% to 60%,[52] whereas the old muscles tended to have curvilinear relationship (hyperbolic curve) between force deficit and strain.[51] These characteristics of eccentric contractions have been exclusively observed in studies performed on rodent EDL muscle or fibers obtained from EDL muscle.[50,53] However, the predominant myosin heavy chain (MHC) isoform in the mouse EDL is type IIb,[54] which is an absent form of the limb muscles of larger mammals, such as humans.[55,56] Therefore, not only are these functional approaches limited by fiber type heterogeneity, but also these species differences could confound generalization of animal data to humans.

Human studies examining the effect of eccentric-induced muscle damage and age do not show consistent results. The increased susceptibility of aged muscle to eccentric contraction was reported following eccentric activities of knee extensor[24] and forearm flexors,[26] and it contributed to the smaller muscle mass and lower maximal oxygen uptake.[24] By contrast, others have reported that the loss of maximal isometric contraction was less for old adults than young adults following voluntary eccentric exercise of the elbow flexors,[27,28] and it contributed to the less degree of muscle damage in older adults due to less mechanical stress during eccentric contraction. These contradictory results of eccentric-induced muscle damage on aging may be due to the inability to adequately control important factors contributing to muscle damage, such as strain magnitude,[29] intramuscular fiber pennation, and motor unit recruitment patterns in human muscle.

The use of chemically skinned permeabilized single fibers allowed us to apply an eccentric contraction, standardized in terms of stain magnitude, and lengthening velocity, to maximally activated cell segments and to subsequently assess the MHC isoform content of these segments. A previous study examined how aging affects the innate susceptibility of muscle cells to high mechanical strain by using single muscle cell preparation.[57] Ca^{2+}-activated force reduction of single skinned muscle fibers prepared from vastus lateralis of elderly human individuals ($n = 10$, age $= 78 \pm 2$ years) were measured before and after single standardized eccentric contraction (25% strain and 50% of maximal shortening velocity). Fiber MHC isoforms were confirmed by sodium dodecyl sulfate polyacrylamide gel electrophoresis. Compared to young fibers, type I fiber showed identical response to eccentric contraction, regardless age group. Otherwise, type IIa and IIa/IIx fibers from old individuals experience greater force reduction than corresponding fibers from young individuals. Therefore, the innate susceptibility of myofilament lattice and cytoskeletal of fast fiber (type IIa and IIa/IIx fiber) of old individuals were more susceptible to a standardized eccentric contraction. By contrast, type I fibers preserved the sensitivity to eccentric contraction regardless of aging. This novel study provides a possible mechanistic explanation for the general characteristic of sarcopenia in which a selective loss of fast-twitch fiber could be originated and/or exacerbated by heightened susceptibility of myofilament lattice and cytoskeletal of fast-twitch fiber in elderly adults. However, note that chemically skinned muscle cell was studied in a non-physiological setting; for example, EC coupling process had been eliminated, and lacks some properties of living cells, such as removed some proteins that confer mechanical stability to the cell, and diffused soluble enzyme, including proteolytic enzymes from the fibers. Therefore, the result may not represent the response during voluntary eccentric activity. Even though the human *in vivo* experimental setting involves all membrane structure and EC coupling process, but they have motor unit recruitment issues and indirect control of strain magnitude.

4. Relationship between eccentric-induced muscle damage and recovery on aged muscle

The increased susceptibility of aged muscle has critical and clinical importance because recovery after eccentric damage is slowed[22,58] or absent[59–61] in muscles of old rodents. In detail, the contractile functions of damaged old muscle did not recover for up to 2 months[22,58] or it could bring about permanent loss of muscle mass and force.[59–61] This lack of recovery is thought to be attributed to impaired muscle regeneration,[59–61] resulting from the reduced number of satellite cells, shortened telomeres, and replicative senescence,[62,63] and the preferential loss of type II fiber.[5] However, it is still unknown how eccentric contraction affects to cross-bridge mechanics during recovery process in the aged muscle cell. Because single muscle fiber preparations can avoid these limitations by allowing the investigator rigorous control over strain magnitude and velocity under well standardized experimental conditions, additional study is clearly required using chemically skinned human muscle fiber prepared from damaged muscle under the *in vivo* experimental setting.

5. Conclusion

In summary, the identification of the etiology of the age-related increase in susceptibility to eccentric-induced muscle damage will be expected to have important clinical significance, because eccentric-induced muscle injury could aggravate the general symptoms of sarcopenia. However, there are few reports investigating the muscle fiber susceptibility and their MHC isoform expression. Thus, additional studies are required to investigate how aged muscle or muscle cells respond to eccentric contraction under physiological conditions.

Conflicts of interest

The author has no conflicts of interest to declare.

Acknowledgments

This research was supported by Kyungsung University Research Grants (Busan, Korea) in 2016.

REFERENCES

1. Doherty TJ. Invited review: aging and sarcopenia. *J Appl Physiol* 2003;95:1717–27.
2. Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, et al. The loss of skeletal muscle strength, mass, and quality in older adults: the health, aging and body composition study. *J Gerontol A Biol Sci Med Sci* 2006;61:1059–64.
3. Lynch GS, Schertzer JD, Ryall JG. Therapeutic approaches for muscle wasting disorders. *Pharmacol Ther* 2007;113:461–87.
4. Thomas DR. Loss of skeletal muscle mass in aging: examining the relationship of starvation, sarcopenia and cachexia. *Clin Nutr* 2007;26:389–99.
5. Larsson L, Grimby G, Karlsson J. Muscle strength and speed of movement in relation to age and muscle morphology. *J Appl Respir Physiol Environ Exerc Physiol* 1979;46:451–6.
6. Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci* 1988;84:275–94.
7. Sato T, Akatsuka H, Kito K, Tokoro Y, Tauchi H, Kato K. Age changes in size and number of muscle fibers in human minor pectoral muscle. *Mech Ageing Dev* 1984;28:99–109.
8. Delbono O. Neural control of aging skeletal muscle. *Aging Cell* 2003;2:21–9.
9. Wang ZM, Messi ML, Delbono O. Sustained overexpression of IGF-1 prevents age-dependent decrease in charge movement and intracellular Ca(2+) in mouse skeletal muscle. *Biophys J* 2002;82:1338–44.
10. Ansved T, Larsson L. Effects of denervation on enzyme-histochemical and morphometrical properties of the rat soleus muscle in relation to age. *Acta Physiol Scand* 1990;139:297–304.
11. D'Antona G, Pellegrino MA, Adami R, Rossi R, Carlizzi CN, Canepari M, et al. The effect of ageing and immobilization on structure and function of human skeletal muscle fibres. *J Physiol* 2003;552:499–511.
12. Lowe DA, Surek JT, Thomas DD, Thompson LV. Electron paramagnetic resonance reveals age-related myosin structural changes in rat skeletal muscle fibers. *Am J Physiol Cell Physiol* 2001;280:C540–7.
13. Ochala J, Dorer DJ, Frontera WR, Krivickas LS. Single skeletal muscle fiber behavior after a quick stretch in young and older men: a possible explanation of the relative preservation of eccentric force in old age. *Pflugers Arch* 2006;452:464–70.
14. Vandervoort AA, Kramer JF, Wharram ER. Eccentric knee strength of elderly females. *J Gerontol* 1990;45:B125–8.
15. Byrne C, Twist C, Eston R. Neuromuscular function after exercise-induced muscle damage: theoretical and applied implications. *Sports Med* 2004;34:49–69.
16. Clarkson PM, Sayers SP. Etiology of exercise-induced muscle damage. *Can J Appl Physiol* 1999;24:234–48.
17. Friden J, Sjostrom M, Ekblom B. Myofibrillar damage following intense eccentric exercise in man. *Int J Sports Med* 1983;4:170–6.
18. Newham DJ, McPhail G, Mills KR, Edwards RH. Ultrastructural changes after concentric and eccentric contractions of human muscle. *J Neurol Sci* 1983;61:109–22.
19. Proske U, Allen TJ. Damage to skeletal muscle from eccentric exercise. *Exerc Sport Sci Rev* 2005;33:98–104.
20. Brooks SV, Faulkner JA. Contractile properties of skeletal muscles from young, adult and aged mice. *J Physiol* 1988;404:71–82.
21. Brooks SV, Opiteck JA, Faulkner JA. Conditioning of skeletal muscles in adult and old mice for protection from contraction-induced injury. *J Gerontol A Biol Sci Med Sci* 2001;56:B163–71.
22. Faulkner JA, Brooks SV, Zerba E. Skeletal muscle weakness and fatigue in old age: underlying mechanisms. *Annu Rev Gerontol Geriatr* 1990;10:147–66.
23. McBride TA, Gorin FA, Carlsen RC. Prolonged recovery and reduced adaptation in aged rat muscle following eccentric exercise. *Mech Ageing Dev* 1995;83:185–200.
24. Manfredi TG, Fielding RA, O'Reilly KP, Meredith CN, Lee HY, Evans WJ. Plasma creatine kinase activity and exercise-induced muscle damage in older men. *Med Sci Sports Exerc* 1991;23:1028–34.
25. Ploutz-Snyder LL, Giamis EL, Formikell M, Rosenbaum AE. Resistance training reduces susceptibility to eccentric exercise-induced muscle dysfunction in older women. *J Gerontol A Biol Sci Med Sci* 2001;56:B384–90.
26. Dedrick ME, Clarkson PM. The effects of eccentric exercise on motor performance in young and older women. *Eur J Appl Physiol Occup Physiol* 1990;60:183–6.
27. Lavender A, Nosaka K. Comparison between old and young men for changes in makers of muscle damage following voluntary eccentric exercise of the elbow flexors. *Appl Physiol Nutr Metabol* 2006;31:218–25.
28. Lavender AP, Nosaka K. Responses of old men to repeated bouts of eccentric exercise of the elbow flexors in comparison with young men. *Eur J Appl Physiol* 2006;97:619–26.
29. McCully KK, Faulkner JA. Characteristics of lengthening contractions associated with injury to skeletal muscle fibers. *J Appl Physiol* 1986;61:293–9.
30. Porter MM, Vandervoort AA, Lexell J. Aging of human muscle: structure, function and adaptability. *Scand J Med Sci Sports* 1995;5:129–42.
31. Yarasheski KE, Exercise. aging, and muscle protein metabolism. *J Gerontol A Biol Sci Med Sci* 2003;58:M918–22.
32. Kimball SR, O'Malley JP, Anthony JC, Crozier SJ, Jefferson LS. Assessment of biomarkers of protein anabolism in skeletal muscle during the life span of the rat: sarcopenia despite elevated protein synthesis. *Am J Physiol Endocrinol Metab* 2004;287:E772–80.
33. Schertzer JD, Plant DR, Ryall JG, Beitzel F, Stupka N, Lynch GS. Beta2-agonist administration increases sarcoplasmic reticulum Ca2+-ATPase activity in aged rat skeletal muscle. *Am J Physiol Endocrinol Metab* 2005;288:E526–33.
34. Delbono O, O'Rourke KS, Ettinger WH. Excitation-calcium release uncoupling in aged single human skeletal muscle fibers. *J Membr Biol* 1995;148:211–22.
35. Höök P, Sriramoju V, Larsson L. Effects of aging on actin sliding speed on myosin from single skeletal muscle cells of mice, rats, and humans. *Am J Physiol Cell Physiol* 2001;280:C782–8.
36. Plant DR, Lynch GS. Excitation-contraction coupling and sarcoplasmic reticulum function in mechanically skinned fibres from fast skeletal muscles of aged mice. *J Physiol* 2002;543:169–76.

37. Frontera WR, Suh D, Krivickas LS, Hughes VA, Goldstein R, Roubenoff R. Skeletal muscle fiber quality in older men and women. *Am J Physiol Cell Physiol* 2000;279:C611–8.
38. Krivickas LS, Suh D, Wilkins J, Hughes VA, Roubenoff R, Frontera WR. Age- and gender-related differences in maximum shortening velocity of skeletal muscle fibers. *Am J Phys Med Rehabil* 2001;80:447–55.
39. Larsson L, Li X, Frontera WR. Effects of aging on shortening velocity and myosin isoform composition in single human skeletal muscle cells. *Am J Physiol* 1997;272:C638–49.
40. Ochala J, Frontera WR, Dorer DJ, Van Hoecke J, Krivickas LS. Single skeletal muscle fiber elastic and contractile characteristics in young and older men. *J Gerontol A Biol Sci Med Sci* 2007;62:375–81.
41. Bottinelli R. Functional heterogeneity of mammalian single muscle fibres: do myosin isoforms tell the whole story? *Pflugers Arch* 2001;443:6–17.
42. Canepari M, Rossi R, Pellegrino MA, Orrell RW, Cobbold M, Harridge S, et al. Effects of resistance training on myosin function studied by the in vitro motility assay in young and older men. *J Appl Physiol* 2005;98:2390–5.
43. Ramamurthy B, Hook P, Jones AD, Larsson L. Changes in myosin structure and function in response to glycation. *FASEB J* 2001;15:2415–22.
44. Frontera WR, Hughes VA, Krivickas LS, Kim SK, Foldvari M, Roubenoff R. Strength training in older women: early and late changes in whole muscle and single cells. *Muscle Nerve* 2003;28:601–8.
45. Korhonen MT, Cristea A, Alén M, Häkkinen K, Sipilä S, Mero A, et al. Aging, muscle fiber type, and contractile function in sprint-trained athletes. *J Appl Physiol* 2006;101:906–17.
46. Slivka D, Raue U, Hollon C, Minchev K, Trappe S. Single muscle fiber adaptations to resistance training in old (>80 yr) men: evidence for limited skeletal muscle plasticity. *Am J Physiol Regul Integr Comp Physiol* 2008;295:R273–80.
47. Trappe S, Gallagher P, Harber M, Carrithers J, Fluckey J, Trappe T. Single muscle fibre contractile properties in young and old men and women. *J Physiol* 2003;552:47–58.
48. Frontera WR, Reid KF, Phillips EM, Krivickas LS, Hughes VA, Roubenoff R, et al. Muscle fiber size and function in elderly humans: a longitudinal study. *J Appl Physiol* 2008;105:637–42.
49. Raue U, Slivka D, Minchev K, Trappe S. Improvements in whole muscle and myocellular function are limited with high-intensity resistance training in octogenarian women. *J Appl Physiol* 2009;106:1611–7.
50. Brooks SV, Faulkner JA. The magnitude of the initial injury induced by stretches of maximally activated muscle fibres of mice and rats increases in old age. *J Physiol* 1996;497:573–80.
51. Lynch GS, Faulkner JA, Brooks SV. Force deficits and breakage rates after single lengthening contractions of single fast fibers from unconditioned and conditioned muscles of young and old rats. *Am J Physiol Cell Physiol* 2008;295:C249–56.
52. Consolino CM, Brooks SV. Susceptibility to sarcomere injury induced by single stretches of maximally activated muscles of mdx mice. *J Appl Physiol* 2004;96:633–8.
53. Zerba E, Komorowski T, Faulkner J. Free radical injury to skeletal muscles of young, adult, and old mice. *Am J Physiol Cell Physiol* 1990;258:C429–35.
54. Danieli-Betto D, Esposito A, Germinario E, Sandonà D, Martinello T, Jakubiec-Puka A, et al. Deficiency of alpha-sarcoglycan differently affects fast- and slow-twitch skeletal muscles. *Am J Physiol Regul Integr Comp Physiol* 2005;289:R1328–37.
55. Ennion S, Sant'ana Pereira J, Sargeant AJ, Young A, Goldspink G. Characterization of human skeletal muscle fibres according to the myosin heavy chains they express. *J Muscle Res Cell Motil* 1995;16:35–43.
56. Smerdu V, Karsch-Mizrachi I, Campione M, Leinwand L, Schiaffino S. Type IIx myosin heavy chain transcripts are expressed in type IIb fibers of human skeletal muscle. *Am J Physiol* 1994;267:C1723–8.
57. Choi SJ, Lim JY, Nibaldi EG, Phillips EM, Frontera WR, Fielding RA, et al. Eccentric contraction-induced injury to type I, IIa, and IIa/IIx muscle fibers of elderly adults. *Age (Dordr)* 2012;34:215–26.
58. McArdle A, Dillmann WH, Mestril R, Faulkner JA, Jackson MJ. Overexpression of HSP70 in mouse skeletal muscle protects against muscle damage and age-related muscle dysfunction. *FASEB J* 2004;18:355–7.
59. Brooks SV, Faulkner JA. Contraction-induced injury: recovery of skeletal muscles in young and old mice. *Am J Physiol* 1990;258:C436–42.
60. Rader EP, Faulkner JA. Effect of aging on the recovery following contraction-induced injury in muscles of female mice. *J Appl Physiol* 2006;101:887–92.
61. Rader EP, Faulkner JA. Recovery from contraction-induced injury is impaired in weight-bearing muscles of old male mice. *J Appl Physiol* 2006;100:656–61.
62. Gibson MC, Schultz E. Age-related differences in absolute numbers of skeletal muscle satellite cells. *Muscle Nerve* 1983;6:574–80.
63. Renault V, Thornell LE, Butler-Browne G, Mouly V. Human skeletal muscle satellite cells: aging, oxidative stress and the mitotic clock. *Exp Gerontol* 2002;37:1229–36.