Aging and its effects on inflammation in skeletal muscle at rest and following exercise-induced muscle injury

Jonathan Peake,1,2 Paul Della Gatta,3 and David Cameron-Smith3

1The University of Queensland, School of Human Movement Studies, Brisbane, Australia; 2The University of Queensland, Centre for Military and Veterans’ Health, Brisbane, Australia; and 3School of Exercise and Nutrition Sciences, Deakin University, Melbourne, Australia

Submitted 30 July 2009; accepted in final form 13 April 2010

The world’s elderly population is expanding rapidly, and we are now faced with significant challenges. Inflammation, which is tightly controlled inflammatory response (4, 56, 135, 140, 143, 119, 120, 173). Evidence is accumulating that rapid and efficient repair of muscle injury requires a well-coordinated and sufficient repair of muscle injury. Macrophage infiltration and the gene expression of certain cytokines are reduced in skeletal muscle of elderly people compared with young people following exercise-induced muscle injury. Further research is required to identify the cause(s) of inflammation in skeletal muscle of elderly people. Additional work is also needed to expand our understanding of the cells, proteins, and transcription factors that regulate inflammation in the skeletal muscle of elderly people at rest and after exercise. This knowledge is critical for devising strategies to restrict sarcopenia, and improve the health of today’s elderly population.

sarcopenia; cytokines; macrophages; exercise

THE AGING POPULATION IS INCREASING dramatically throughout the world. Current estimates predict that by 2050, the world’s elderly population (>60 yr) will have tripled from 650 million at present to 2 billion (168). This trend presents special health challenges, which include assisting the elderly population to maintain or improve physical activity, independence, and quality of life. Skeletal muscle mass decreases by 1–2% each year beyond the age of 50 (72, 136). This process is commonly referred to as “sarcopenia.” Importantly, sarcopenia is a key factor contributing to frailty, loss of functional mobility and independence (62, 73), and mortality in the elderly (105, 121).

Inflammation may represent a key factor contributing to sarcopenia (10, 30, 51, 57, 132, 133, 159). Numerous age-related diseases that are associated with sarcopenia also increase inflammation, such as obesity and Type 2 diabetes mellitus (30, 108, 109, 133), dementia (20), heart failure (154), and rheumatological diseases (7). In addition to the role of the immune system in the pathophysiology of these diseases, the immune system itself changes with age. Inflammation generally increases with age, as indicated by higher systemic concentrations of cytokines and acute-phase proteins (50, 169), greater basal (i.e., unstimulated) cytokine production by peripheral blood mononuclear cells in vitro (129), and prolonged inflammatory reactions to infectious challenge in vivo (24, 79, 98). This phenomenon of chronic low-grade inflammation with aging has been termed “inflamm-aging” (53).

Inadequate repair and maladaptation to injury may also contribute to a decline in muscle mass with aging. Injury is more likely to occur, and muscle regeneration is delayed in skeletal muscle of elderly humans/animals compared with young humans/animals (16, 17, 56, 60, 96, 97, 100, 101, 117, 119, 120, 173). Evidence is accumulating that rapid and efficient repair of muscle injury requires a well-coordinated and tightly controlled inflammatory response (4, 56, 135, 140, 143, 150, 161–163). Inappropriate inflammatory responses to muscle injury could explain long-term deterioration of muscle mass and function in the elderly.

In this review, we describe the state of inflammation in skeletal muscle of elderly people at rest and discuss the local and systemic factors that could account for this inflammation. We then compare inflammatory reactions to exercise-induced muscle injury in young and old muscle and discuss the import-
tance of inflammation for the regeneration of injured muscle tissue.

Evidence for a Role of Inflammation in Sarcopenia

Our current understanding of the role of inflammation in sarcopenia is derived from several avenues of research: 1) studies correlating inflammation and sarcopenia, 2) studies of cultured muscle cells or fibers in the presence of inflammatory mediators, and 3) animal models of inflammatory diseases that influence individual factors involved in regulating muscle mass. Surprisingly little research has examined the inflammatory state of skeletal muscle in elderly humans. Cell culture and animal models may not reflect the complex, unpredictable interactions between genes and the environment that form the basis of aging and longevity in humans (53). Several studies have used gene profiling to identify gene clusters and individual genes in muscle that change with age (42, 43, 57, 126, 152, 166). Few of these studies, however, have focused specifically on genes and signaling proteins that regulate inflammation. Below, and in Table 1, we review existing research on age-related differences in the expression of cytokine/chemokine genes and signaling proteins in skeletal muscle at rest. We also briefly discuss the potential role of these factors in sarcopenia.

Proinflammatory cytokines linked to sarcopenia. Evidence as to whether mRNA expression of IL-1β and TNF-α in skeletal muscle increases with age is inconclusive (Table 1) (66, 86, 118, 122). IL-6 and TGF-β mRNA expression is similar in muscle homogenate samples from young and elderly males (66, 110, 118, 155). In contrast, mRNA expression of IL-6 receptor and TGF-β receptor III is higher in muscle homogenate samples from elderly men compared with young men (166). The expression of neutrophil chemoattractant-1 protein is also greater in muscle homogenate samples from old rats compared with young rats (56).

Numerous studies have examined the role of IL-1β, TNF-α, IL-6, and TGF-β on muscle protein breakdown using in vitro cell culture and animal models. In vitro, IL-1β stimulates IL-6 mRNA expression and proteolysis in C2C12 myotubes by activating p38 MAPK and NF-κB, and the atrophy genes atrogen-1/MAFbx and MuRF-1 (87, 95). Degens (39) has published a comprehensive review on the effects of TNF-α on muscle atrophy; therefore, in this review, we have presented only a short summary of the main effects of TNF-α. Many studies have reported that treatment of C2C12 myoblasts and human myoblasts with TNF-α reduces the expression of several genes (e.g., MYOD1, myogenin, p21, and IGF-1) and signaling proteins (e.g., mTOR, S6K1, and 4E-BP1) that regulate protein translation (32, 54, 63, 148, 171). TNF-α stimulates apoptosis to a greater extent in muscle precursor cells from old rats compared with muscle precursor cells from old rats.

Table 1. Age-related differences in the expression of genes and proteins in muscle homogenate samples obtained at rest

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex/Species; Age Difference</th>
<th>Variable</th>
<th>Comparison of Elderly vs. Young</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genes/proteins upregulated in skeletal muscle of elderly humans/animals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(118) Males: mean age 71 yr vs. 32 yr</td>
<td>IL-1β mRNA</td>
<td>+3.3×*</td>
<td></td>
</tr>
<tr>
<td>(86) Males: mean age 70 yr vs. 20 yr</td>
<td>IL-1ra mRNA</td>
<td>+7.2×*</td>
<td></td>
</tr>
<tr>
<td>(75) Males: 62–75 yr vs. 20–34 yr</td>
<td>IL-10 mRNA</td>
<td>+1.4×*</td>
<td></td>
</tr>
<tr>
<td>(172) Males: 51–79 yr vs. 15–38 yr</td>
<td>TNF-α mRNA</td>
<td>+2.8×*</td>
<td></td>
</tr>
<tr>
<td>(25) Males: mean age 64 yr vs. 21 yr</td>
<td>SOCS3 mRNA</td>
<td>+1.5×*</td>
<td></td>
</tr>
<tr>
<td>(152) Males and females: mean age 73 yr vs. 37 yr</td>
<td>SOCS3 total protein</td>
<td>+1.5×*</td>
<td></td>
</tr>
<tr>
<td>(64) Rats: 30 mo vs. 6 mo</td>
<td>HSP27 mRNA</td>
<td>+2.7×*</td>
<td></td>
</tr>
<tr>
<td>(56) Rats: 24 mo vs. 2 mo</td>
<td>NK cell enhancing factor mRNA</td>
<td>+2.8×*</td>
<td></td>
</tr>
<tr>
<td>Genes/proteins not altered in skeletal muscle of elderly humans/animals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(118) Males: mean age 71 yr versus 32 yr</td>
<td>HSP70 total protein</td>
<td>+1.5×*</td>
<td></td>
</tr>
<tr>
<td>(155) Males: mean age 67 yr versus 20 yr</td>
<td>p50B-crystallin total protein</td>
<td>+61%*</td>
<td></td>
</tr>
<tr>
<td>(66) Males: 66–78 yr 23–35 yr</td>
<td>NF-κB p65</td>
<td>+14%*</td>
<td></td>
</tr>
<tr>
<td>(66) Males: 66–78 yr 23–35 yr</td>
<td>NF-κB p50</td>
<td>+26%*</td>
<td></td>
</tr>
<tr>
<td>(66) Males: 66–78 yr 23–35 yr</td>
<td>SOCS3 mRNA</td>
<td>+40%*</td>
<td></td>
</tr>
<tr>
<td>(152) Males and females: mean age 73 yr vs. 37 yr</td>
<td>CINC-1</td>
<td>+10.6×*</td>
<td></td>
</tr>
<tr>
<td>(118) Males: mean age 71 yr versus 32 yr</td>
<td>IL-6 mRNA</td>
<td>+3.3×*</td>
<td></td>
</tr>
<tr>
<td>(118) Males: mean age 71 yr versus 32 yr</td>
<td>IL-6 mRNA</td>
<td>+7.2×*</td>
<td></td>
</tr>
<tr>
<td>(118) Males: mean age 71 yr versus 32 yr</td>
<td>IL-6 mRNA</td>
<td>+1.4×*</td>
<td></td>
</tr>
<tr>
<td>(122) Females: 85 yr vs. 23 yr</td>
<td>TNF-α mRNA</td>
<td>+2.8×*</td>
<td></td>
</tr>
<tr>
<td>(118) Males: mean age 71 yr vs. 32 yr</td>
<td>TGF-β mRNA</td>
<td>+1.5×*</td>
<td></td>
</tr>
<tr>
<td>(155) Males: mean age 67 yr vs. 20 yr</td>
<td>TGF-β protein</td>
<td>+2.7×*</td>
<td></td>
</tr>
<tr>
<td>(152) Males and females: mean age 73 yr vs. 37 yr</td>
<td>SOCS3 mRNA</td>
<td>+40%*</td>
<td></td>
</tr>
<tr>
<td>(25) Males: mean age 64 yr vs. 21 yr</td>
<td>SOCS3 total protein</td>
<td>+10.6×*</td>
<td></td>
</tr>
<tr>
<td>IL, interleukin; ra, receptor antagonist; NK, natural killer; HSP, heat shock protein; AMAC, alternative macrophage activation-associated chemokine. TNF, tumor necrosis factor; TGF, transforming growth factor; SOCS, suppressor of cytokine signaling. CINC-1, neutrophil chemoattractant protein 1. IsxBα, inhibitor of κBα. NF-κB, nuclear factor κB. *Significantly different between young and elderly, P &lt; 0.05.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
young rats (74, 85). These findings suggest that sensitivity to TNF-α may increase with age.

In vivo, TNF-α induces muscle wasting in healthy rodents (83, 93), and rodents with conditions, such as cancer cachexia (35, 63, 145), chronic pulmonary inflammation (82), and sepsis (81). The findings from these animal studies are also supported indirectly by observations in elderly humans. Bruunsgaard et al. (21) found that the plasma concentration of soluble TNF-α receptor 1 was inversely correlated with muscular strength. Taekema et al. (151) reported that TNF-α synthesis in whole blood correlated with decreasing grip strength over a 4-year period. Finally, Griewe et al. (61) also observed that TNF-α mRNA expression in muscle homogenate was inversely correlated with muscle protein synthesis following a period of resistance training.

Contrary to the findings described above, other in vitro research findings suggest that under certain conditions, TNF-α can promote muscle protein synthesis. The effects of TNF-α on muscle protein degradation or synthesis may depend on the state of cell differentiation, as well as other factors present in the local environment. TNF-α protects myoblasts from apoptosis (89), but it induces apoptosis in myotubes (146). TNF-α also causes greater apoptosis in skeletal muscle with a higher proportion of type II fibers compared with muscle comprising mainly type I fibers (115). Plaisance et al. (116) demonstrated that in primary myotubes, low doses of TNF-α (1 ng/ml) stimulated maximal protein synthesis within 24 h. In contrast, they observed that in C2C12 myotubes, a higher dose of TNF-α (50 ng/ml) was required to induce maximal protein synthesis, and protein synthesis increased for more than 48 h. Differences in the number and kinetics of the expression of TNF-α receptor 1 on the surface of these two cell types may account for these variable effects of TNF-α (116). Warren et al. (161) found that the effects of TNF-α on muscle mass in vivo also vary according to the phase of muscle regeneration. Specifically, muscular isometric strength was similar between TNF-α knockout mice compared with wild-type mice 5 days after muscle injury, whereas muscular isometric strength was significantly lower in TNF-α knockout mice compared with wild-type mice 13 days after muscle injury. These findings indicate that TNF-α plays a key role during later phases of muscle regeneration (i.e., >1 wk).

The effects of TNF-α on protein synthesis may also depend on the concentration of TNF-α, and other factors present in the local environment. Most of the studies described above are in vitro cell culture studies (54, 55, 63, 74, 85, 116, 148, 171). Within these studies, the dose of TNF-α applied to cells varied between 1 and 100 ng/ml; this variation could explain some of the contrasting effects of TNF-α. Currently, insufficient data are available to establish whether a threshold exists for the concentration TNF-α that regulates the balance between muscle protein synthesis and degradation. Al-Shanti et al. (1) demonstrated that on its own, TNF-α (10 ng/ml) did not influence survival or proliferation of C2C12 myoblasts. When cells were incubated with TNF-α for 24 h, and IL-6 (2.5 ng/ml) for a further 24 h, cell survival increased almost twofold, and cell proliferation increased threefold, whereas cell differentiation did not change. These findings suggest that IL-6 may modulate the effects of TNF-α on muscle cell growth. Plaisance et al. (116) have suggested that IGF-1 may mediate the effects of TNF-α on protein synthesis/degradation; however, the interaction between IGF-1 and proinflammatory cytokines, such as TNF-α under conditions of muscle atrophy and/or regeneration, is unclear (40, 111).

The lack of any age-related difference in IL-6 mRNA expression in human skeletal muscle (66, 110, 118, 155) is somewhat surprising, considering the role that IL-6 plays in regulating muscle mass. Several studies have reported that infusion or overexpression of IL-6 increases muscle atrophy in mice (65, 147, 156). Haddad et al. (65) demonstrated that 14 days of intramuscular infusion of IL-6 reduced total protein content and myofibrillar content in tibialis anterior in rats. This effect was associated with increased mRNA expression of suppressor of cytokine signaling (SOCS3) SOCS3, activation of STAT3, and inhibition of S6K1 activity (65). Similarly, Tsujinaka et al. (157) observed that blocking the IL-6 receptor in IL-6 transgenic mice prevented muscle atrophy, and attenuated mRNA and protein expression of cathepsin B, cathepsin L, monoubiquitins, and polyubiquitins. Some of these effects may be linked to defective signaling through growth hormone and IGF-1 signaling pathways (10, 37, 91).

These findings contrast markedly with other research, indicating that similar to TNF-α, IL-6 can also promote muscle growth under certain conditions. Muscle hypertrophy is lower in IL-6 knockout mice compared with wild-type mice as a result of reduced satellite cell-derived myonuclear accretion (138). In human muscle homogenate samples collected after exercise, IL-6 colocalized with Pax7+ satellite cells, and the number of IL-6+/Pax7+ cells correlated with the number of Pax7+/PCNA+ (proliferating cell nuclear antigen) cells (r = 0.52, P < 0.0001) (102). Data from several in vitro cell culture studies support these findings. Baeza-Raja and Munoz-Canoves (5) observed that recombinant IL-6 (dose not stated) stimulated C2C12 myoblasts to differentiate. Furthermore, short interfering RNA against IL-6 prevented myoblast differentiation. Al-Shanti et al. (1) have also demonstrated that IL-6, in combination with TNF-α stimulated growth of C2C12 myoblasts by activating the gp130 and IGF-1 receptors. IL-6 also stimulates myoblast proliferation in vitro by activating STAT3 (138).

Variation within the experimental models used to examine the role of IL-6 in regulating muscle mass makes it difficult to compare the results of different studies. On the basis of the data available, it would seem that overexpression of IL-6 stimulates muscle atrophy, whereas IL-6 insufficiency inhibits muscle growth. The effects of IL-6 on muscle mass may depend on changes in the activity of other genes and transcription factors (e.g., IGF-1, SOCS, STAT) in response to high vs. low concentrations of IL-6 in the local microenvironment within skeletal muscle.

The lack of any difference in mRNA expression of TGF-β in muscle homogenate samples from elderly vs. young people (66) is also surprising. Similar to TNF-α, TGF-β inhibits the proliferation of myogenic cells both in vitro and in vivo (28, 88). Furthermore, TGF-β stimulates myoblasts to differentiate into myofibroblasts in vitro (29) and in vivo (88). This process is mediated through signaling pathways that involve the Smad protein family, sphingosine kinase, and sphingosine 1-phosphate (29). This process may account for the decrease in fibrosis in skeletal muscle of elderly humans/animals (14). In contrast with TGF-β itself, expression of TGF-β receptor III is higher in muscle homogenate samples from elderly men com-
pared with young men (166). This increase may be functionally important, because TGF-β receptors inhibit the myogenic activity of satellite cells (28). In addition to TGF-β, IFN-γ regulates the growth and differentiation of muscle cells (34, 131). To date, no research has investigated changes in the expression and activity of IFN-γ in skeletal muscle with age to determine whether it plays a role in sarcopenia.

**Anti-inflammatory cytokines.** IL-1α and IL-10 mRNA expression is elevated in muscle homogenate samples from elderly males compared with young males (118). The source of these anti-inflammatory cytokines is unclear, however, because the number of anti-inflammatory macrophages (CD163+) tends to be lower in muscle homogenate samples from elderly men (118). The increased mRNA expression of IL-1α and IL-10 in skeletal muscle of elderly people may reflect an anti-inflammatory response to the increased gene expression of IL-1β (118). IL-10 inhibits the proteolytic effects of IL-1β in muscle cells (149).

**Other inflammatory mediators.** A number of factors regulate inflammation in skeletal muscle, including NF-κB, SOCS3, and peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1). Heat shock proteins and reactive oxygen and nitrogen species regulate inflammation indirectly by altering the activity of these transcription factors and genes. NF-κB is a key regulator of inflammation in skeletal muscle (2). The protein abundance of NF-κB subunits (e.g., IKK-γ, IkBa, p50, and p65) is greater in muscle homogenate samples from old rats (26 mo) compared with young rats (6 mo) (115), as well as in muscle homogenate samples from elderly people compared with young people (25, 152). Coupled with increased expression of these subunits, NF-κB binding activity is elevated in muscle homogenate samples from old mice (26–28 mo) compared with adult mice (10–12 mo) (19). Inactivity (9, 45, 46) and high dietary calorie intake (115) may both contribute to the rise in NF-κB activity that occurs in skeletal muscle with age.

SOCS3 regulates NF-κB activity and IL-6 gene expression in C2C12 myotubes (144). Whether SOCS3 expression and activity in skeletal muscle change with age is uncertain. Two studies have reported greater expression of SOCS3 mRNA and total protein in muscle homogenate samples from elderly men compared with young men (86), and old rats compared with young rats (64). In contrast, other research has failed to demonstrate any differences in SOCS3 mRNA and total protein expression in muscle homogenate samples from young and elderly men (155). These inconsistent findings regarding changes in the expression of SOCS3 with age may be related to differences between studies with regard to the age, sex, and habitual physical activity of study participants. Alternatively, species differences between humans and rats may also account for these differences.

PGC-1 regulates inflammation within skeletal muscle. Evidence that PGC-1 regulates inflammation within skeletal muscle is that compared with wild-type mice, mice lacking the muscle-specific isoform of PGC-1α express greater amounts of TNF-α, IL-6, CD68, SOCS1, and SOCS3 mRNA in muscle homogenate samples (67, 68). Conversely, overexpression of PGC-1α reduces mRNA expression of TNF-α and IL-6 in myotubes (68) and prevents muscle atrophy in mouse skeletal muscle by inhibiting NF-κB activity, apoptosis, and proteolysis (167). The gene expression of PGC-1 is lower in muscle homogenate samples from old rats (30–40 mo) compared with adult rats (8–10 mo) (6), and elderly humans (~60 years) compared with young humans (~30 years) (92). Collectively, these findings suggest that lower expression of PGC-1 genes may contribute to chronic low-grade inflammation in skeletal muscle of elderly people.

Heat shock proteins and reactive oxygen and nitrogen species indirectly regulate inflammation by altering NF-κB activity in muscle cells (3, 78, 90) and whole muscle (3, 19, 45, 46, 137). The expression of heat shock protein 27 (HSP27), αβ-crystallin, and HSP70 proteins is elevated in muscle homogenate samples from elderly humans (152, 172), and old rodents (26–28 mo) (19, 45). Increased expression of heat shock proteins in skeletal muscle with age may help to counteract inflammation and oxidative stress (19, 45, 137). Oxidative stress in skeletal muscle also increases with age, as indicated by low glutathione content, increased antioxidant enzyme activity, increased expression of gp91phox, lipid peroxidation, and DNA damage in muscle homogenate samples from elderly humans/animals compared with young humans/animals (19, 31, 56, 104, 160, 165, 166). This DNA damage may, in turn, increase proinflammatory cytokine synthesis, apoptosis, and fibrosis in skeletal muscle cells and neighboring cells (70, 125).

**Causes of Inflammation in Skeletal Muscle**

In the previous section of this review, we described the inflammatory state of skeletal muscle of elderly people and discussed some of the regulatory factors that contribute to this inflammatory state. Below, we discuss some of the potential causes and cellular sources of inflammation in skeletal muscle in the elderly. Inflammation in skeletal muscle may result from local inflammatory reactions, and/or systemic “spill over” of inflammatory mediators from other organs.

Intermuscular adipose tissue content and intramyocellular lipid deposits increase with age (36, 41, 106, 174), and this adipose tissue appears to replace muscle tissue (142). Intermuscular adipose tissue may accumulate in skeletal muscle of elderly people as a result of satellite cells differentiating into adipogenic cells (38, 71, 131, 134, 139). Satellite cells can also differentiate into fibroblasts (14). Both adipocytes and fibroblasts produce proinflammatory cytokines and growth factors (58, 99), and these cell types may contribute to the inflammatory state of skeletal muscle in the elderly. Macrophage numbers are higher in muscle homogenate samples from obese people compared with lean people (158). Furthermore, TNF-α mRNA, SOCS3 mRNA, toll-like receptor (TLR) 4, and JNK proteins are elevated in muscle homogenate samples of people with Type 2 diabetes compared with lean people (8, 123, 124). Increased fat mass and insulin resistance may, therefore, explain, at least in part, the observations that TNF-α mRNA, TLR4 mRNA, SOCS3, and JNK proteins are expressed in greater abundance in muscle homogenate samples from elderly people compared with young people (80, 86, 170).

The circulating concentrations of cytokines and C-reactive protein are often elevated in people with age-related diseases, including obesity and Type 2 diabetes (30, 108, 109, 133), atherosclerosis (23), dementia (20), osteoporosis (44), rheumatoid arthritis (7), and chronic heart failure (69). Local inflammation in adipose, vascular, and synovial tissues is a causative factor in all of these disease states (11, 13, 48, 59, 107, 164),
but it is unclear whether “spillover” of inflammatory cytokines and reactive oxygen/nitrogen species from these tissues into the circulation also causes inflammation in other tissues, such as skeletal muscle.

Macrophages and other cells in visceral adipose tissue are a likely source of systemic inflammation that is observed in obese people and those with Type 2 diabetes (30, 108, 109, 133). Macrophages, fibroblasts, and vascular endothelial cells produce inflammatory mediators locally in vascular and synovial tissues (12, 15, 47); however, the cellular sources of systemic inflammation in atherosclerosis (23), dementia (20), osteoporosis (44), rheumatoid arthritis (7), and chronic heart failure (69) are more difficult to identify. Systemic inflammation in elderly people may, therefore, depend on several factors, including the presence of any chronic diseases, the severity of such diseases, and cross-talk (stimulatory and inhibitory) between diseased tissues. Independent of age-related diseases, chronic low-grade inflammation with age may also result naturally from repeated exposure to bacterial and viral infections (53).

Aging, Muscle Injury, and Inflammation

Tissue regeneration following injury is delayed in skeletal muscle of elderly humans/animals (17, 60, 100, 117, 119, 120, 173). Regular resistance training improves resistance to injury in skeletal muscle of elderly humans/animals, but this adaptive process occurs more slowly in skeletal muscle of elderly humans/animals compared with young humans/animals (18, 84, 96, 101, 117, 127, 128). We speculate that slower repair and adaptation of skeletal muscle of elderly people may result from chronic inflammation and stress. In support of this concept, Ghaly and Marsh (56) reported greater fibrosis 3 wk after contusion injury in muscle homogenate samples from old rats compared with young rats. On a long-term basis, inadequate repair of skeletal muscle of elderly people tissue may lead to the perpetual cycle of disuse and muscle atrophy that characterizes sarcopenia (49). Surprisingly few studies have compared the systemic and local inflammatory responses to exercise-induced muscle damage in young and elderly people (Table 2).

Systemic inflammatory responses. Circulating neutrophil counts are lower 6 h after 45 min downhill running in elderly men (55–74 yr) compared with young men (20–32 yr) (26, 27). This response may be due to greater auto-oxidation of neutrophils with aging, as supplementation with 400 IU vitamin E tocopherol daily for 48 days before exercise corrects this age-related difference in neutrophil counts following exercise-induced muscle damage (26). Plasma IL-6 concentration is also lower 4 h after 1 h eccentric cycling in elderly men (67–75 yr) compared with young men (20–27 yr) (153).

One possible reason for these findings is that chronic low-grade inflammation limits the capacity of immune cells to respond to additional inflammatory stimuli. Two lines of evidence support this concept. First, cytokine responses to in vitro stimulation of whole blood with lipopolysaccharide are suppressed in elderly people compared with young people (22). Second, in response to pneumococcal infection (24) and in vivo infusion of lipopolysaccharide (2 ng/kg body mass) (79), the plasma concentrations of TNF-α, sTNF-αR1, and C-reactive protein increase more rapidly, and remain elevated for a longer period of time in elderly people compared with young people.

In contrast with the findings of the studies described above (26, 27, 153), another exercise study reported no differences in neutrophil counts or plasma IL-6 concentration between young (18–35 yr) and elderly men (65–80 yr) after 45 min downhill running (130). The reasons for this disparity are unclear but may include differences between these exercise studies (26, 27, 130, 153) regarding the intensity and mode of exercise, the age, and habitual physical activity of the study participants. The plasma concentrations of IL-1ra, sTNF-αR1, TGF-β, and C-reactive protein increased similarly after exercise in both young and elderly men (130, 153). These findings suggest that not all systemic inflammatory reactions to exercise-induced muscle injury change with age.

Local inflammatory responses. Macrophage infiltration is lower in muscle homogenate samples from elderly men compared with young men following exercise-induced muscle injury (66, 118). Lower numbers of macrophages in skeletal muscle of elderly people may inhibit muscle regeneration following injury. Macrophages regulate the mRNA expression of TNF-α, MCP-1, and IGF-1, and restrict necrosis, lipid accumulation, and fibrosis in regenerating muscle (4, 135, 143, 150). During muscle regeneration, macrophages also interact with myogenic precursor cells by means of direct cell-cell adhesion, thereby rescuing them from apoptosis (33, 143). As muscle regeneration proceeds, macrophages switch phenotype from proinflammatory cells that stimulate phagocytosis and myogenic cell proliferation to anti-inflammatory cells that stimulate myogenesis and fiber growth (4), and recruit satellite cells (94). The findings described above for macrophage responses to exercise-induced muscle injury in humans (66, 118) contrast with the results of Ghaly and Marsh (56). This group reported greater macrophage and neutrophil infiltration in muscle homogenate samples from old rats compared with young rats following contusion injury. This disparity may be related to differences in the type of injury, or species differences. Other research implicates HSP70 (76, 100) and PGC-1 (67) as important factors that regulate muscle regeneration following injury.

The effects of age on cytokine/chemokine responses to exercise-induced muscle injury are variable. After exercise, TNF-α mRNA in skeletal muscle either increases to a similar degree (66) or remains unchanged in young and elderly people (122). There are reports that IL-6 mRNA after exercise is greater (155), lower (66), or similar (118) in muscle homogenate samples from elderly men compared with young men. After exercise, IL-1β mRNA in muscle homogenate samples is either lower in elderly men (75, 118) or increases to the same degree in young and elderly men (66). Alternative macrophage activation-associated chemokine-1 mRNA increases in muscle homogenate samples from young men, but not elderly men, after exercise (118). Ghaly and Marsh (56) reported greater expression of TGF-β1 protein and NF-κB p65 8 h and 3 days after contusion injury in muscle homogenate samples from old rats compared with young rats. SOCS3 mRNA is higher, whereas SOCS3 protein is lower after exercise in muscle homogenate samples from elderly men compared with young men (155). In contrast, SOCS3 mRNA and protein expression is similar in skeletal muscle of adult and old rats after isometric muscle contractions (64). The variability in these inflammatory processes is likely due to differences in the intensity and mode of exercise, the age, and habitual physical activity of the study participants. The plasma concentrations of IL-1ra, sTNF-αR1, TGF-β, and C-reactive protein increased similarly after exercise in both young and elderly men (130, 153). These findings suggest that not all systemic inflammatory reactions to exercise-induced muscle injury change with age.
Review

AGING AND INFLAMMATION IN SKELETAL MUSCLE

Table 2. Age-related differences in the expression of genes and proteins in muscle homogenate samples obtained following exercise in humans or stimulated muscle contractions or contusion injury in rats

<table>
<thead>
<tr>
<th>Reference</th>
<th>Sex/Species: Age Difference</th>
<th>Exercise/Contraction Protocol; Time of Muscle Sampling</th>
<th>Variable</th>
<th>Comparison of Elderly Vs. Young</th>
</tr>
</thead>
<tbody>
<tr>
<td>(155)</td>
<td>Males: mean age 67 yr vs. 20 yr</td>
<td>3 sets of 8 reps, knee extensions at 100% 1 RM; 2 h later</td>
<td>SOCS3 mRNA</td>
<td>Increased 16× in elderly; 6× in young</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>IL-6 mRNA</td>
<td>Increased 156× in elderly; 3× in young</td>
</tr>
<tr>
<td>(56)</td>
<td>Rats: 24 mo vs. 2 mo</td>
<td>Contusion injury; 3 days later</td>
<td>TGF-β1 protein</td>
<td>Increased 1.6× in old rats; no change in young rats*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NF-κB p65</td>
<td>Increased 1.6× in old rats; increased 40% in young rats*</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>CINC-1</td>
<td>Increased 1.1×; no change in young rats*</td>
</tr>
</tbody>
</table>

Response to exercise increased in skeletal muscle of elderly humans/animals

<table>
<thead>
<tr>
<th>Reference</th>
<th>Exercise/Contraction Protocol; Time of Muscle Sampling</th>
<th>Variable</th>
<th>Comparison of Elderly Vs. Young</th>
</tr>
</thead>
<tbody>
<tr>
<td>(66)</td>
<td>45 min downhill running at −16% gradient; 3 days later</td>
<td>CD18 mRNA</td>
<td>Increased 4.7× in elderly; 10× in young*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-6 mRNA</td>
<td>No change in elderly; increased 3.6× in young†</td>
</tr>
<tr>
<td>(118)</td>
<td>3 sets of 8 reps, one set to failure, leg exercise at 80% 1 RM; 3 days later</td>
<td>IL-1β mRNA</td>
<td>No change in elderly; increased 2× in young†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IL-10 mRNA</td>
<td>No change in elderly; increased 2× in young†</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AMAC-1 mRNA</td>
<td>No change in elderly; increased 2× in young†</td>
</tr>
<tr>
<td>(75)</td>
<td>3 sets of 8 reps of leg exercise at 80% 1 RM; 1 day later</td>
<td>NK cell enhancing factor mRNA</td>
<td>No change in elderly; increased 3.4× in young†</td>
</tr>
</tbody>
</table>

Response to exercise attenuated in skeletal muscle of elderly humans/animals

<table>
<thead>
<tr>
<th>Reference</th>
<th>Exercise/Contraction Protocol; Time of Muscle Sampling</th>
<th>Variable</th>
<th>Comparison of Elderly Vs. Young</th>
</tr>
</thead>
<tbody>
<tr>
<td>(155)</td>
<td>3 sets of 8 reps, knee extensions at 100% 1 RM; 2 h later</td>
<td>SOCS3 protein</td>
<td>Increased 6× in elderly; 18× in young</td>
</tr>
<tr>
<td></td>
<td>3 sets of 8 reps of leg exercise at 80% 1 RM; 1 day later</td>
<td>IL-1β mRNA</td>
<td>Increased 1.4× in elderly; 3.5× in young</td>
</tr>
<tr>
<td>(66)</td>
<td>45 min downhill running at −16% gradient; 3 days later</td>
<td>IL-1β mRNA</td>
<td>Increased 1.9× in elderly; 4.5× in young</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HSP27 mRNA</td>
<td>Increased 2.8× in elderly males; 1.7× in young males</td>
</tr>
<tr>
<td>(118)</td>
<td>3 sets of 8 reps, one set to failure, leg exercise at 80% 1 RM; 3 days later</td>
<td>IL-6 mRNA</td>
<td>No change in elderly or young</td>
</tr>
<tr>
<td></td>
<td>3 maximal isometric contractions per minute, 4 s duty cycle/16 s rest for 30 min; 24 h and 48 h later</td>
<td>SOCS3 mRNA</td>
<td>Increased 100% in old rats; 3× in adult rats</td>
</tr>
</tbody>
</table>

Response to exercise similar in young and elderly

RM, repetition maximum. See Table 1 for other definition of abbreviations. *Significantly different between young and elderly; †significant change only in young group; ‡significant change only in elderly group, P < 0.05.

Following muscle injury, TNF-α, the chemokines MCP-1, IL-8, and GM-CSF, and COX-2 accelerate muscle repair by recruiting neutrophils and macrophages, reducing the expression of TGF-β mRNA, and increasing MyoD mRNA expression (112, 113, 140, 141, 161, 163). IL-6 does not play an acute role in repairing muscle injury (161), but it is involved in muscle hypertrophy (1, 138). Relatively little is known about the anti-inflammatory response to exercise-induced muscle damage in skeletal muscle of elderly people. Anti-inflammatory reactions are essential for muscle repair and growth (4, 94, 149). IL-10 mRNA expression is lower in muscle homogenate samples from elderly men compared with young men after resistance exercise, whereas IL-1ra mRNA remains unchanged in skeletal muscle in both young and elderly men (118). Following treatment with LPS, IL-6 mRNA expression in skeletal muscle is elevated in IL-10 knockout mice compared with wild-type mice. This effect is greater in mature mice (10–11 mo) compared with young mice (4 mo) (103). These
findings highlight the importance of anti-inflammatory cytokines, such as IL-10 in regulating inflammation in skeletal muscle of elderly people. Future research could investigate changes in other anti-inflammatory cytokines (e.g., IL-4 and IL-13) in skeletal muscle after exercise-induced muscle injury to determine whether, in addition to IL-10, these cytokines also orchestrate muscle tissue regeneration. Together, these data support the concept that rapid and efficient repair of muscle injury requires a well-coordinated and tightly controlled inflammatory response. This response may decrease with age, resulting in chronic maladaptation to muscle injury (56).

**Perspectives and Significance**

Most of our current knowledge on the relationships between inflammation and sarcopenia is derived from epidemiological studies that have correlated systemic markers of inflammation with low muscle mass, physical inactivity, and frailty. Only a small number of studies have directly assessed the state of inflammation in skeletal muscle of elderly people. The paucity of knowledge that currently exists concerning how inflammation in skeletal muscle changes with age highlights the need for further research on the following issues. First, we need to focus on the cause(s) of inflammation in resting skeletal muscle. This will require a greater focus on the pluripotent effects of age-related diseases such as Type 2 diabetes mellitus, obesity, atherosclerosis, heart failure, and rheumatoid arthritis. Second, we need to examine in greater detail the phenotype and functional activity of macrophages in skeletal muscle of elderly people, because macrophages are key regulators of apoptosis and remodeling in skeletal muscle. Third, we need to assess whether the expression of chemokines (e.g., MCP-1, IL-8, RANTES) and anti-inflammatory cytokines (e.g., IL-4, IL-10, IL-13) changes with age. These factors play central roles in resolving inflammation and repairing muscle tissue following injury. Lastly, we need to expand our understanding of the signaling pathways that regulate inflammation in skeletal muscle of elderly people at rest and following injury. These pathways include those involving Toll-like receptors, calcineurin/nuclear factor of activated T cells, and NF-kB. We also need to dedicate more attention to investigating the benefits of diet and regular exercise training to reduce inflammation in skeletal muscle of elderly people. Exercise training, particularly resistance training, is effective for maintaining skeletal muscle mass in the elderly (77). Exercise training is also effective for reducing systemic inflammation (52, 114). Less is known about the benefits of exercise training for reducing local inflammation within skeletal muscle of elderly people (61, 80). More research is required to establish the most effective forms of exercise training (i.e., resistance or aerobic, or a combination of both), and the potential additive effects of dietary modification for reducing inflammation in skeletal muscle of elderly people. Reducing inflammation in skeletal muscle will help to restrict muscle atrophy, improve muscular strength, and reduce the risk of falls in elderly people. These benefits of exercise training and dietary modification will become critical over the course of the next 40 years, during which the world’s elderly population is expected to grow dramatically.

**DISCLOSURES**

No conflicts of interest, financial or otherwise, are declared by the authors.

**REFERENCES**


AGING AND INFLAMMATION IN SKELETAL MUSCLE

Review

R1493


100. Meador B, Krzysztof C, Johnson R, Huey K. Effects of IL-10 and age on IL-6, IL-1β, and TNFα responses in mouse skeletal and cardiac...


Strassmann G, Fong M, Kenney JS, Jacob CO.

Taekema DG, Westendorp RG, Frolich M, Gussekloo J.


Thalacker-Mercer A, Dell'italia LJ, Cui X, Cross JM, Bamman MM.


Trenerry MK, Carey KA, Ward AC, Farnfield MM, Cameron-Smith.


