

Leucocytes, cytokines and satellite cells: what role do they play in muscle damage and regeneration following eccentric exercise?

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ABSTRACT

Exercise-induced muscle damage is an important topic in exercise physiology. However, several aspects of our understanding of how muscles respond to highly stressful exercise remain unclear. In the first section of this review we address the evidence that exercise can cause muscle damage and inflammation in otherwise healthy human skeletal muscles. We approach this concept by comparing changes in muscle function (i.e., the force-generating capacity) with the degree of leucocyte accumulation in muscle following exercise. In the second section, we explore the cytokine response to 'muscle-damaging exercise', primarily eccentric exercise. We review the evidence for the notion that the degree of muscle damage is related to the magnitude of the cytokine response. In the third and final section, we look at the satellite cell response to a single bout of eccentric exercise, as well as the role of the cyclooxygenase enzymes (COX1 and 2). In summary, we propose that muscle damage as evaluated by changes in muscle function is related to leucocyte accumulation in the exercised muscles. 'Extreme' exercise protocols, encompassing unaccustomed maximal eccentric exercise across a large range of motion, generally inflict severe muscle damage, inflammation and prolonged recovery (> 1 week). By contrast, exercise resembling regular athletic training (resistance exercise and downhill running) typically causes mild muscle damage (myofibrillar disruptions) and full recovery normally occurs within a few days. Large variation in individual responses to a given exercise should, however, be expected.

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The link between cytokine and satellite cell responses and exercise-induced muscle damage is not so clear. The systemic cytokine response may be linked more closely to the metabolic demands of exercise rather than muscle damage. With the exception of IL-6, the sources of systemic cytokines following exercise remain unclear. The satellite cell response to severe muscle damage is related to regeneration, whereas the biological significance of satellite cell proliferation after mild damage or non-damaging exercise remains uncertain. The COX enzymes regulate satellite cell activity, as demonstrated in animal models; however, the roles of the COX enzymes in human skeletal muscle need further investigation. We suggest using the term 'muscle damage' with care. Comparisons between studies and individuals must consider changes in and recovery of muscle force-generating capacity.

Keywords: Skeletal muscle, lengthening contractions, ultrastructural disruptions, necrosis, myokines, cyclooxygenase (COX1, COX2), non-steroidal anti-inflammatory drugs (NSAIDs)

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INTRODUCTION

Exercise-induced muscle damage has been a popular topic in exercise science for many years. In particular, the term ‘delayed onset muscle soreness’ (DOMS) has been a recurring theme since the early work of Hough (127) (e.g., (3,12,15,66,68,123,210)). Human studies investigating the physiological responses to eccentric exercise (i.e., lengthening muscle actions) were conducted as early as the end of the 19th century and the beginning of the 20th century (references in (16)). More controlled experiments on eccentric exercise (e.g., ‘backwards’ cycling) were conducted by Abbott *et al.* (1,2) and Asmussen (16) in the 1950’s. Extending the pioneering work of Hill (21,122), Katz (144) carefully explored the basic physiology of muscle lengthening. Concerning the potential for eccentric muscle actions to cause muscle damage, Katz wrote: ‘Rapid stretching of an active muscle, beyond its optimum length, is apt to break or weaken permanently parts of the contractile substance’ (p. 64, (144)). Important research into muscle physiology and sarcomere and myofibrillar mechanics continued through the work of Gordon, Huxley and Julian (108,109,132,133), and later Julian and Morgan (140,141). Morgan (205) put forward the ‘popping sarcomere hypothesis’ to explain the observations of disruptions to the myofibrillar machinery of skeletal muscle fibres after eccentric actions (reviews: (5,206,207,245)). Many other investigators have contributed to the paradigm of exercise-induced muscle damage, but some worth mentioning for their significant contributions include Salmiinen and Vihko (258-260,306,307), Armstrong *et al.* (11,12,14,315), Faulkner *et al.* (37,88,89), McArdle and Jackson (134,186-188), and Fridén and Lieber (157-159). These investigators mainly worked with muscle preparations (*in vitro* studies) and animals models (e.g., rodents and rabbits). Work on humans at the myocellular level was initiated by Fridén *et al.* (96,97,101-103) and Newham *et al.* (137,210,213) in the 1980’s. These authors investigated the effects of downstairs running, eccentric (backwards) cycling, stepping exercise (one eccentric working leg), isolated eccentric work for the elbow flexors and backward walking on a treadmill (targeting the calf muscles). They reported disruptions at the ultrastructural level and more gross cellular damage, comprising leucocyte accumulation and regeneration. Thereby, they confirmed many of the findings from previous studies on muscle preparation and animals. During the last few decades researchers have, with ever more advanced techniques, attempted to understand the aetiology of exercise-induced muscle damage. This work has focused on mechanical tearing, metabolic stress, the local and systemic inflammatory response, as well as the recovery process involving satellite cell activation and muscle regeneration (64,86,170,232,247,275,292,296,298).

In the first part we review the evidence for muscle damage and local inflammation (i.e., accumulation of leucocytes in the muscle tissue) following various types of eccentric exercise. In general, the assessment of muscle damage requires reliable and valid markers. This is indeed a major challenge, because in human research there are currently no markers that are considered the ‘gold standard’. Histological observations (light or electron microscopy) and changes in muscle function (force-generating capacity) seem to be the most valid markers of muscle damage, although both have some limitations. Histological examination of muscle biopsy samples (typically, sections cut from a 5–20 mg muscle sample) can

identify abnormalities such as myofibrillar disruptions and the presence of inflammatory cells. However, the question remains as to whether this small piece is representative of the whole muscle (12,26,316). Changes in force-generating capacity are an indirect measure of muscle damage. Nevertheless, with appropriate testing, changes in muscle function give a good indication of the status of the whole muscle (316). Muscle damage is therefore best assessed by measuring changes in force-generating capacity and performing histological observations. Other proxy markers of muscle damage, such as DOMS and circulating creatine kinase (CK), are generally not considered sufficiently valid (66,280,316), but do provide some additional or complementary information. In this section, we focus on the relationships between changes in muscle function and histological evidence for myofibrillar disruptions, inflammation and myofibre necrosis in human studies.

In the second part of this review, we look at the exercise-induced cytokine response. The systemic inflammatory response comprises a leucocytosis and an acute-phase response (86). Cytokines (e.g., IL-1 and IL-6) are part of the acute-phase response, and strenuous exercise generally seems to increase the circulating levels of a number of different cytokines. Cytokines are traditionally regarded as messenger molecules associated with leucocytes and inflammatory and immunological reactions. However, more recent research demonstrates that these cytokines are not only produced by leucocytes, but also by myofibres and peritendinous tissue (151,238). This had led to the term ‘myokines’, which refers to muscle-derived cytokines and chemokines. Uncertainty persists concerning the physiological actions and the precise source of production for cytokines found in the circulation during and after exercise. We have reviewed the literature for studies that have investigated the cytokine/myokine response in relation to eccentric exercise.

In the final part of this review, we describe the satellite cell response to single bouts of eccentric exercise. Satellite cells are undeniably required for regeneration of gross muscle damage where segments of myofibres are lost, for example, after a strain injury with torn myofibres (136). Surprisingly, satellite cells seem responsive to a variety of exercise protocols, both muscle damaging and non-damaging exercise. We review the satellite cell response to eccentric exercise. Non-steroidal inflammatory drugs that inhibit the activity of cyclooxygenase enzymes in skeletal muscle can also inhibit the satellite cell response. We discuss the evidence for this effect in humans.

1. DEFINING EXERCISE-INDUCED MUSCLE DAMAGE

Regular exercise generally makes our muscles stronger and/or more resistant to fatigue. However, during intense exercise our muscles fatigue and weaken temporarily. If the exercise is unaccustomed and/or very vigorous, we may even damage the working muscles, and it may take days for the muscles to recover. This type of muscle damage has been named ‘exercise-induced muscle damage’ (143,226). Various types of eccentric exercise (i.e., lengthening muscle actions) have been used to induce muscle damage experimentally (49,64,86,282). Exercise-induced muscle damage also occurs after long distance running (121,272,273,310) and to some degree after traditional resistance exercise (i.e.,

lifting weights; (94,251,281,308))—especially if the exercise is unaccustomed, very intense and/or too frequent (69,148,194). However, exercise-induced muscle damage does not have any established definition; it is merely characterised by a set of signs and symptoms (49,66,159,282). DOMS is the most common symptom of exercise-induced muscle damage, whereas histological evidence of disruptions of the myofibrillar structure and, especially, myofibre necrosis and inflammation are the ultimate signs of muscle damage (if we disregard methodological uncertainties; discussed below).

Necrotic cells go through several stages (304), but necrotic segments of myofibres may appear as swollen and rounded (on cross-sections). Immunohistochemical staining for cytoskeletal (e.g., desmin and dystrophin) and myofibrillar proteins (myosin) is diminished (or absent), which indicates degradation of these proteins (71,158,166). Disruption of the sarcolemmal membrane causes influx of extracellular proteins, such as fibronectin and albumin (72,283). Segmental myofibre necrosis¹ is manifested by inflammatory cells (particularly macrophages) that have invaded these myofibres and accumulation of myoblasts that originate primarily from satellite cells ((136,154,158,230,257,284); see also Figure 1). Because necrotic cells will attract immune-competent cells through receptors, such as toll-like receptors (50,78,184), accumulation of inflammatory cells within myofibres is a strong sign of segmental myofibre degradation and necrosis.

Some studies have reported signs of necrosis in voluntarily exercised muscles of seemingly healthy subjects (72,74,121,135,137,226,230,310). In rare cases, experimental subjects and patients have been diagnosed with rhabdomyolysis after exercise. Rhabdomyolysis is broadly defined by severe muscle pain/tenderness, swelling and muscle weakness, elevated blood activity of muscle proteins such as CK (> 10,000 IU/L), and dark urine, indicating myoglobinuria (65,146,264,271). Serious cases of rhabdomyolysis (including myoglobinuria) have been observed after various types of exercise, but rhabdomyolysis has been most frequently reported after extreme military training (135,262).

In experiments involving eccentric exercise, relatively little evidence of severe myofibre necrosis exists (Table 1; see addendum). A more common finding is accumulation of inflammatory cells, primarily monocytes/macrophages, in the endomysium and especially in the perimysium ((92,119,129,229,283); see also Table 1). However, in response to 'extreme' exercise massive leucocyte infiltration and cellular accumulation inside myofibres can be demonstrated (60,224,230,257). These observations suggest that the leucocytes are recruited to remove cellular debris and prepare for regeneration of necrotic segments of myofibres (56,85). Thus, necrotic myofibre segments seem to induce a strong chemotactic signal to recruit leucocytes; however, exercised muscle tissue may also summon leucocytes in the absence of necrosis (Figure 1—moderate damage versus severe damage).

Leucocytes may start to infiltrate the muscle tissue immediately after exercise, but are typically detected in the extracellular space 24–48 hours after exercise (25,92,119,229). They infiltrate the intracellular space ~4–7 days after exercise—if some myofibres become necrotic (60,229,230). Leucocyte accumulation therefore appears to be a gradual process regulated by the extent of damage. In response to severe damage, leucocyte accumulation peaks in time with the pres-

¹ 'Segmental myofibre necrosis' implies that there are segments or parts of the fibre that are necrotic, not necessarily the whole myofibre (99,136,158).

ence of necrotic myofibres (60,137,229,230,257). In relation to muscle function, McCully and Faulkner (192) have reported a high correlation between gross muscle damage (apparent cellular infiltrate and myofibre necrosis) and reduction in the force-generating capacity.

Another histological characteristic of muscles following eccentric exercise is myofibrillar disruption. Fridén *et al.* (102,103) provided the first evidence of morphological changes in the 'contractile machinery' after eccentric exercise in humans (running down stairs and eccentric cycling). No gross damage or leucocytes were seen by light microscopy, but electron microscopy revealed subcellular disorganisation of the myofibrillar structure, especially that of the Z-bands (Z-band streaming and smearing (98)). Several subsequent studies have verified these findings (105,106,126,182,213,250), with (154,226,229) and without (71,223,324) simultaneous signs of inflammation and necrosis. Myofibrillar disruption is strongly associated with structural changes to the t-tubule system and the sarcolemma (245,289,315). Note that myofibrillar disruptions have been reported immediately after exercise, as well as one week after exercise, whereas the greatest disturbances are typically found after 1–4 days (103,121,213,250,325).

Whether myofibrillar disruptions indicate damage or remodelling and incorporation of new sarcomeres is debatable (71,97,126,154,213,324,325). Sarcomere disruption and myofibrillar disorganisation are linked to reduced force-generating capacity (106,154,162,176,250), and sarcomeres are disrupted following single eccentric muscle actions (39). These findings suggest that the myofibrillar disruption that occurs during or shortly after exercise represents damage. The changes in myofibrillar structures observed some days into recovery may, however, more appropriately be termed 'remodelling' (325). Minor myofibrillar disruptions can indeed occur without significant changes in the force-generating capacity (105,245). These findings raise the question of whether initial damage due to mechanical forces and activation of Ca^{2+} -dependent proteinases (e.g., calpain (161,250)) are required for remodelling. Nevertheless, disruption of intracellular Ca^{2+} regulation probably links myofibrillar damage with necrosis. Hence, if Ca^{2+} homeostasis is not re-established within a few days after exercise, the damage to the myofibrillar structure and the cytoskeleton may become irreparable, and segments of the myofibre become necrotic (Figure 1 and (5,98,107,245)).

Limited human research has examined changes to the extracellular matrix in response to eccentric exercise, but intracellular and extracellular events appear to occur simultaneously (40,73,173,250). Stauber *et al.* (283) reported that the extracellular matrix was separated from the myofibres after exercise. More recent studies have observed increased expression of tenascin C and PIINP², which indicate remodelling of the extracellular matrix (73,250). Damage to the extracellular matrix may increase permeability of the sarcolemmal membrane, as indicated by increased efflux of CK and myoglobin, and influx of albumin and tetranectin (280,283,319).

Reports from various animal models show that exercise-induced muscle damage is linked to inflammation (88,200,274,275,296). Humans, however, can experience symptoms of exercise-induced muscle damage, such as DOMS and increased passive tension, without presenting classical signs of inflammation (i.e., leucocyte infiltration) in the muscle tissue (71,180,229,230,251). Based on

² N-terminal propeptide of Type III procollagen

well-controlled experiments, some researchers claim that voluntary eccentric exercise does not cause gross muscle damage (necrosis) or cellular infiltration in the exercised muscles (71,178,179,326). This concept challenges the validity of a series of human studies from the late 1980's and the 1990's (e.g., (60,92,119,137,226,257)). The main criticism of these classical 'muscle damage' studies is the risk of bias resulting from repeated biopsies from the same muscle (179). Malm *et al.* (180) reported no differences in leucocyte infiltration in muscle samples obtained from eccentrically-exercised muscle and resting muscle up to one week after exercise. Based on these observations they argued that the biopsy procedure itself, rather than exercise, increased inflammation in muscle. Electrical stimulation of human skeletal muscles causes significantly more damage than voluntary exercise (71,171). For these reasons, some researchers (71,179) also question the relevance of data from animal studies using rather 'non-physiological' muscle actions to inflict massive/gross muscle damage.

These problems arising from repeated biopsies, together with the results from electrical stimulation of human muscle, challenge the paradigm of exercise-induced muscle damage. Historically, this paradigm has been based on data from animal studies, and has muscle damage and inflammation as fundamental events (see introduction and (10,12,14,158,200)). Nevertheless, more recent studies that have collected samples from both exercised and resting muscle provide compelling evidence that eccentric exercise can lead to both accumulation of leucocytes and myofibre necrosis (154,229,230). Importantly, large variations in the individual responses to eccentric exercise were evident, and gross muscle damage did not occur in all individuals (229,230). The literature on exercise-induced muscle damage is therefore full of contradictory reports (e.g., see Table 1). Some of this variability is simply due to non-specific nomenclature used to identify and describe 'muscle damage' and inflammation.

Other confounding factors in this debate on exercise-induced muscle damage include variation in exercise protocols and inconsistent measurements of muscle function (i.e., the force-generating capacity) to assess muscle damage. Malm *et al.* (180,181) and Yu *et al.* (326) reported no signs of necrosis or inflammation after submaximal, eccentrically-biased exercise (i.e., backwards cycling, downhill running and running down stairs). Although they observed severe DOMS after these exercise protocols, changes in other markers of muscle damage were rather trivial compared with observations reported by others (e.g., (60,137,283)). Specifically, Malm *et al.* (181) reported that isometric strength (torque) decreased by only 15% in the first 24 hours after exercise. Isometric strength then returned to normal in the following 24 hours. Serum CK activity increased, but only about six times above pre-exercise values. By contrast, in other studies in which high-force eccentric exercise across large ranges of motion was used, isometric/concentric force-generating capacity decreased by about 50% after exercise. Recovery of muscle function in these other studies was also significantly slower, and plasma/serum CK activity reached more than 100 times pre-exercise values (see Table 1). These contrasting findings raise the question of whether it is appropriate to compare cellular responses from studies using quite different exercise protocols.

2. CHANGES IN MUSCLE FUNCTION REFLECT THE EXTENT OF MUSCLE DAMAGE

To assess muscle damage directly, histological analysis of muscle tissue is required (88). However, collecting tissue samples from humans can be unpleasant for the subjects and demanding on resources. Histological analysis of human muscle tissue can also be unreliable (26,115,156,316). For these reasons, proxy markers of muscle damage such as DOMS, range of motion, swelling, and serum CK activity are often used. But these markers do not always accurately reflect the extent of muscle damage, and do not always correlate with each other (100,128,210,218,219,255,280,316). By contrast, muscle function measured as force-generating capacity (e.g., maximal concentric or isometric strength) is relatively easy to measure, and is generally considered to be a reliable and valid marker for the degree of muscle damage (49,64,88,98,245).

Studies that have both obtained biopsies and measured changes in muscle function are summarised in Table 1 (see addendum). These studies point to an association between changes in force-generating capacity and histological observations such as myofibrillar disruptions, signs of necrosis and leucocyte accumulation. In those studies that report a minor reduction in the force-generating capacity (< 20% of pre-exercise values; Table 1A), few or no morphological/histological abnormalities are found. By contrast, those studies that report a large reduction in muscle function (> 50%; Table 1C) also report inflammation (leucocyte accumulation) and/or segmental myofibre degradation/necrosis. Eccentrically-biased exercise (e.g., downhill running) generally causes smaller changes in muscle function compared with isolated, eccentric muscle actions that involve a large range of motion (Table 1 and 2; see addendum).

Eccentrically-biased exercise and isolated eccentric exercise differ with regard to the mechanical characteristics of muscle-damaging exercise. The most critical factors for muscle damage are high force and large strain (i.e., muscle lengthening beyond the optimum length for force-generation (29,39,112,160,176,212,290,291)). Eccentric exercise that involves a large range of motion and high force-generation is very likely to cause substantial structural (myofibrillar) disruptions, and in turn, reduced muscle function. Other factors, such as joint angle velocity (51,52,192,227,312) and number of repetitions (41,162,219,221,291) may modify the degree of muscle damage. However, these factors seem secondary to the work (strain $\times$ force [J]) done to lengthen/stretch the muscles (38,88,167,321).

2.1 Mild exercised-induced muscle damage

Among those studies that report a relatively small reduction in the force-generating capacity (i.e., < 20%) and rapid recovery (33,71,90,181), only one study reported accumulation of leucocytes in the tissue ((71); Table 1A; see addendum). None of these studies observed any signs of necrosis, and plasma/serum CK activity did not surpass $\sim 1,000$ IU/L.

In the study by Bourgeois *et al.* (33), subjects exercised with a load equal to 80–85% of 1RM (i.e., traditional resistance exercise), whereas in the study of Feasson *et al.* (90) and Malm *et al.* (181), subjects ran downhill (on a treadmill). In the study of Cramer *et al.* (71), subjects completed a bout of unilateral, single joint (knee), maximal eccentric actions. Compared with studies that have used

similar protocols (24,25,201), the reduction of muscle function was surprisingly low in the study by Crameri *et al.* (71). Nevertheless, Crameri *et al.* (71) did observe both myofibrillar disruption and accumulation of macrophages (CD68+ cells). Interestingly, the contralateral leg completed the same number of eccentric actions, but was stimulated electrically (not shown in Table 1A). Compared with the voluntarily exercised muscle, the electrically-stimulated muscle was clearly damaged. Necrosis was indicated by accumulation of intracellular leucocytes (CD68+ cells) and myofibres that did not express desmin or dystrophin. The authors suggested that these variations may be due to differences in the pattern of muscle activation between voluntary and electrically-stimulated muscle actions (71).

Although increased numbers of leucocytes are not found (by immunohistochemistry) within muscle fibres after these exercise protocols, it does not exclude the possibility that there are interactions between the exercised myofibres and the immune system. Circulating leucocytes may indeed accumulate in the micro-vessels of the exercised muscles (229). Raastad *et al.* (251) used radionuclide imaging (which involves radiolabelling of autologous leucocytes—primarily neutrophils—and scintigraphy). They documented an early accumulation of leucocytes in muscle 1–24 hours after resistance exercise. The force-generating capacity decreased by 16% shortly after exercise and returned to normal between 28 and 47 hours after exercise, indicating only mild muscle damage. Based on this evidence, we propose that the immune system immediately responds to muscle damage resulting from the stress of high-force exercise. However, when muscle damage is mild, blood borne leucocytes do not leave the circulation in significant numbers (229). Although there is no accumulation of leucocytes in the muscle tissue after exercise, resident stromal cells, such as macrophages, may become activated, and thereby play a role in the recovery and adaptation to exercise (246). Evidence to support this notion awaits further experiments on human subjects.

Figure 2 (upper curve) demonstrates typical changes in the force-generating capacity of trained subjects that have performed a bout of a heavy traditional resistance exercise (3–8 repetition maximum) or subjects that are ‘low responders’ to eccentric exercise. Typically the reduction in the force-generating capacity after exercise is less than 20% and recovery is completed within 48 hours. We suggest using the term ‘mild exercise-induced muscle damage’ if the reduction in the force-generating capacity is less than 20% and/or recovery is completed within 48 hours after exercise.

2.2 Moderate exercise-induced muscle damage

Among those studies reporting a moderate reduction in the force-generating capacity (20–50%), only one study reported signs of necrosis (229), but five (24,25,129,229,287) of eight studies found accumulation of leucocytes in the exercised muscles (Table 1B; see addendum). Two of the three studies that did not report increased numbers of leucocytes also reported the smallest reduction in the force-generating capacity.

Paulsen *et al.* (229) reported very high serum CK activity in some subjects, and intracellular accumulation of leucocytes in four of eleven subjects. Although this histological observation was very infrequent (~1% of the counted fibres), it indicates that some degree of segmental necrosis did occur. Of note, tissue sam-

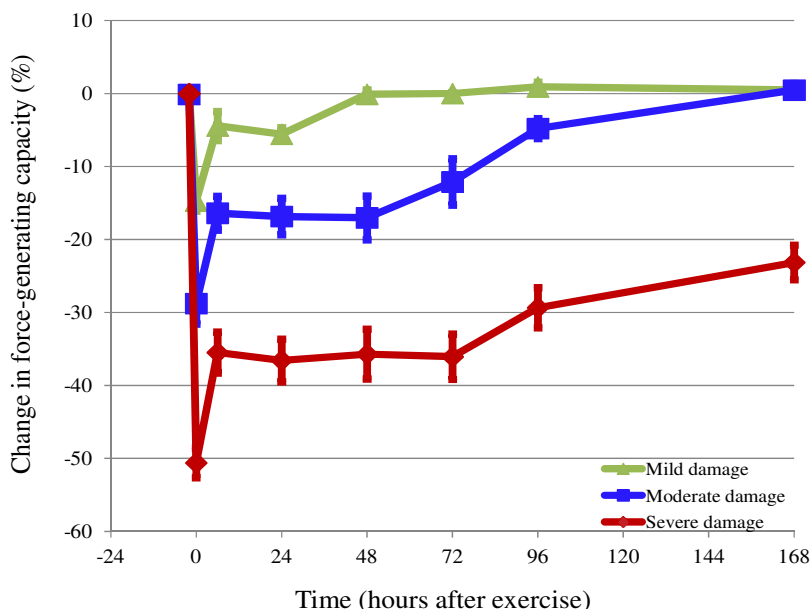


Figure 2. Recovery of the force-generating capacity of subjects that have performed heavy resistance exercise or maximal eccentric exercise (subjects from several studies are combined: (230,248-251), as well as unpublished data). The subjects are organized so that those who recover their force-generating capacity within 48 hours are represented as mild exercise-induced muscle damage (34 subjects). Those who recover between 2 and 7 days are presented as moderate exercise-induced muscle damage (17 subjects). Finally, subjects that do not recover within one week are presented as severe exercise-induced muscle damage (21 subjects). See further comments in the text. All data are gathered at the Norwegian School of Sport Sciences by Professor Truls Raastad. Data are presented as means $\pm$ standard error of the mean.

ples that exhibited intracellular leucocyte accumulation were typically collected from 'high responder' subjects who showed a substantial decline in muscle function (50–73% lower immediately after exercise, and 17–42% lower 1 week later), indicating they had suffered severe muscle damage.

Beaton *et al.* (25) did not observe necrotic myofibres, but did observe reduced immunohistochemical staining of both desmin and dystrophin, as well as increased numbers of macrophages between myofibres 4 and 24 hours after exercise. It is likely that necrosis was not evident at these early time points. The authors suggested that these findings were related to increased activity of the Ca^{2+} -dependent calpain system, as mentioned in Figure 1.

Figure 2 (middle curve) demonstrates the typical recovery of the force-generating capacity in subjects that have performed unaccustomed eccentric exercise and some subjects that have performed heavy traditional resistance exercise. We suggest using the term 'moderate exercise-induced muscle damage' if the largest reduction in the force-generating capacity is between 20–50%, and/or recovery is completed between 2 and 7 days after exercise.

2.2 Severe exercised-induced muscle damage

All studies reporting large loss of force-generating capacity ($\geq 50\%$ reduction) and long-lasting recovery (> 1 week) also reported accumulation of leucocytes in the exercised muscle tissue, and all but one found signs of segmental myofibre necrosis (Table 1C; see addendum). All studies that assessed serum/plasma CK activity also observed high CK activity (i.e., subjects with values $> 10,000$ IU/L). Although changes in CK activity have been reported to correlate poorly with other damage markers in some studies (100,182,280), very high CK activity does appear to accompany severe reductions in force-generating capacity (218,229) and evidence of severe muscle damage (137). Changes in CK activity in these cases follow a similar time course to histological observations of severe muscle damage (about 4 days after exercise; (60,137,230)). Thus, CK activity measurements may be used to separate subjects with mild muscle damage ($< 1,000$ IU/L) and severe muscle damage ($> 10,000$ IU/L; (66)). Considering the combination of reduced muscle function and increased CK activity with severe soreness and massive muscle swelling after exercise, many of the subjects in these studies would probably be diagnosed with rhabdomyolysis if they had attended an emergency room.

Muscle samples from subjects with very severe exercise-induced muscle damage may display a long-lasting regeneration process between 1 and 3 weeks after exercise (137,154,230,257). Increased numbers of macrophages (or other CD68 positive stromal cells) are present even after 3 weeks, but these cells are primarily located in the extracellular matrix around regenerated myofibres (230). The regeneration process therefore exceeds 3 weeks, and corresponds with incomplete recovery of muscle function at this time point. Sayers and Clarkson (263) have reported recovery times of 33–47 days for subjects with an immediate reduction in muscle function of $> 70\%$ after eccentric exercise with the elbow flexors. Foley *et al.* (93) observed that muscle volume of the elbow flexors decreased by about 10% for a period from 2–8 weeks after eccentric exercise. These two studies did not obtain muscle biopsies; but it seems very likely that necrosis of myofibres delayed muscle recovery and caused significant atrophy of the exercised muscles. The cross-sectional area of regenerating fibres is typically much smaller compared with undamaged adjacent myofibres 2–3 weeks after exercise (137,230,281).

Myofibrillar disruption was evident in several of the studies in Tables 1 (A–C) that also reported minor changes in muscle function. It appears that myofibrillar disruption is not directly—or at least not linearly—related to the accumulation of leucocytes. Some studies indicate that myofibrillar disruption can occur in the absence of leucocyte accumulation (90,103,326). Other studies, however, do show a significant correlation between myofibrillar disruption and leucocyte accumulation (92,229). Therefore, we suggest that when intracellular damage exceeds a certain level, leucocytes accumulate in the damaged tissue. The factors that regulate this degree of damage could include degradation and damage to the sarcolemma. As myofibrillar disruption worsens during the first days after exercise (probably due to failure to re-establish intracellular Ca^{2+} -homeostasis), the cytoskeletal framework eventually collapses, thereby leading to sarcolemmal damage (245). Significant leakage of intracellular proteins to the extracellular milieu stimulates inflammation (22,79,95,295). If the remodelling process fails to

restore the subcellular structure within a few days, further damage occurs and eventually segments of myofibers will become necrotic (Figure 1—severe damage).

Figure 2 (lower curve) displays the typical time course of changes in the force-generating capacity for subjects who do not recover within one week after exercise. Such changes are exclusively observed after unaccustomed eccentric exercise and are typically observed together with high circulating CK activity, histological signs of myofibrillar damage and leucocyte accumulation. We suggest using the term ‘severe exercise-induced muscle damage’ if the greatest reduction in the force-generating capacity is larger than 50%, and/or recovery is not completed within 7 days after exercise.

2.3 Muscle damage is dependent on the choice of exercise protocol

Unfortunately, relatively few studies investigating inflammation in muscle following exercise have examined changes in muscle function. However, it is possible to assess the degree of damage by considering the exercise protocols that were used in these studies (Table 2; see addendum). For the studies summarised in Tables 1A–C and Tables 2A and B, resistance exercise (with equal concentric and eccentric loads) and eccentrically-biased exercise, such as downhill running (~8°) and running down stairs (33,90,102,181,223,326), generally do not cause severe muscle damage or significant leucocyte accumulation in the exercised muscles. By contrast, tissue accumulation of leucocytes occurs consistently after single joint, maximal eccentric exercise across a large range of motion (24,25,60,137,177,283,320). Stepping exercise (i.e., isolated eccentric work for one leg (213,224)), very steep downhill running (e.g., 16° in Fielding *et al.* (92)) and very long distance running (74,121) appear to induce moderate or severe muscle damage and leucocyte accumulation (at least if the exercise is unaccustomed). Studies involving eccentric cycling have produced mixed findings (103,119,150,180,226).

Although single joint, maximal eccentric exercise across a large range of motion usually inflicts considerable muscle damage, responses to this form of exercise do vary. MacIntyre *et al.* (168,169) used an exercise protocol that consisted of 300 eccentric knee-extensions. Several other more recent studies have adopted this protocol (20,25,71,209,229). MacIntyre *et al.* (168) and Murphy *et al.* (209) observed that force-generating capacity decreased only moderately by 20–25% immediately after exercise. In the latter study, recovery was actually complete between 3 and 24 hours after exercise. By contrast, Paulsen *et al.* (229) and Beaton *et al.* (25) found that force-generating capacity decreased by about 50% shortly after exercise, and was about 30% below baseline at 48 hours after exercise. These measurements of muscle function point to differences between studies at the cellular level, despite the similarities in exercise protocol. The reasons for the rather large differences between studies are difficult to determine, but we provide some plausible explanations below.

2.4 Low and high responders make interpretations difficult

The differences between studies (Table 1 and 2; see addendum) are a challenge for understanding the physiology and/or pathology behind exercise-induced muscle damage. The inter-individual variation in each study is also problematic, especially in stud-

ies with low subject numbers. Large inter-individual variation in response to eccentric exercise is commonly reported (54,58,67,113,131,211,218,229,263,265,268). Individuals are sometimes characterised as 'low', 'medium/moderate' or 'high' responders, based on changes in muscle function (229,265), CK activity (58) and signs of necrosis and regeneration (230). The factors contributing to this interesting phenomenon are uncertain. One possibility is that so-called 'low-responders' show less impairment of muscle function because they have recently (i.e., within some months (220)) performed high-force eccentric work using the same muscle(s) (commonly referred to as the 'repeated-bout effect' (194)). Other contributing factors to the large variation in individual responses may include: age (53,138,155,183), gender (63,263,287), certain genetic factors (62,81,82,130,323) and training status (10,87,105,229,308), as well as flexibility (57,195), eccentric peak and end-range torque (265) and angle of peak torque (cf. the joint angle-torque relationship (207)). In combination with wide variation in exercise protocols and challenges with the biopsy analyses (26), this unpredictable inter-individual variability may explain much of the diverse findings and debate on the aetiology of exercise-induced muscle damage. Future studies on exercise-induced muscle damage should consider these factors. The most important action would probably be to carefully evaluate the number of subjects needed. Probably no more than one third of individuals are likely to be 'high' responders who display a clear local inflammatory reaction—even when using maximal voluntary eccentric exercise across a wide range of motion (72,229,230).

We would like to emphasise that using traditional statistics such as means and standard deviations to describe and illustrate the response to eccentric exercise can mask important and interesting observations, because of large inter-individual variations. We recommend to report individual data and classifying subjects as 'low', 'moderate' and 'high' responders, because this will allow for better presentation and interpretation of the data (229,265). Therefore, studies on exercised-induced muscle damage should be designed (with power estimations) for detecting different responders.

2.5 Inconsistencies between animal studies and human studies

The data summarised in Tables 1 and 2 (see addendum) suggest that a certain level of damage is required to initiate a detectable inflammatory reaction with leucocyte accumulation in exercised muscle tissue. This level of damage seems rather high, because it is mainly unaccustomed maximal eccentric exercise that induces extensive muscle damage and inflammation. By contrast, more applied modes of exercise, such as traditional resistance exercise, cause less or no gross muscle damage and inflammation.

Somewhat surprisingly, the relationship between the degree of muscle damage and inflammation (leucocyte accumulation) in animals seems even less clear. In experiments with rodents, leucocyte accumulation is evident after passive stretches and isometric actions that supposedly do not cause damage (147,164,243), and also after low mechanical impact exercises, such as swimming (208) and level running (252). Hence, there appears to be important differences between humans and (caged) mice with respect to exercise-induced muscle damage. Although the sequence of events is similar in humans and animals after muscle damaging exercise, the time course seems much faster in animals. For exam-

ple, in humans, plasma/serum CK activity and histological abnormalities seem to peak after 4–7 days (67,154,210,229,230), whereas in typical animal models, these events occur 1–3 days after exercise (13,37,100,153,192,193,204). These observations suggest that caution is advised when comparing data on inflammatory reactions to exercise-induced muscle damage between humans and animals.

Summary

Exercised-induced muscle damage is characterised by a set of symptoms and signs ('damage markers'). These markers typically include DOMS, increased passive tension, decreased range of motion, increased levels of circulating proteins such as CK and myoglobin, and decreased force-generating capacity (muscular strength), as well as histological evidence of myofibrillar disruption, cellular infiltration, and necrosis. The presence and severity of the different symptoms/signs varies widely between studies. A troubling fact is the relatively weak association between these damage markers (219,229,255,280,316). For example, DOMS does not reflect histological observations of myofibrillar disruptions or accumulation of inflammatory cells. However, as others have suggested (88,316), changes in muscle function appear to be the best marker for the degree of exercise-induced muscle damage. Although the capacity to activate the exercised muscles may change in the recovery phase (27,42,244), reduced force-generating capacity seems to reflect myofibrillar disruption, inflammation and necrosis better than any other markers of muscle damage. Based on our review of the literature, we suggest the following scheme for assessing the extent of muscle damage:

- 'mild exercise-induced muscle damage' corresponds with a decline in force-generating capacity of no more than 20% (during the first 24 hours), and/or full recovery within 48 hours;
- 'moderate exercise-induced muscle damage' corresponds with a 20–50% decline in force-generating capacity, and/or full recovery between 48 hours and 7 days;
- 'severe exercise-induced muscle damage' corresponds with a decline in force-generating capacity of more than 50%, and/or that recovery of force-generating capacity exceeds 1 week.

We further suggest that muscle function should be assessed as concentric actions at a slow velocity, e.g., 30–60°/s, and across a large range of motion. Peak torque, total work and angle of peak torque should be reported. Isometric contractions may also be used, but exercise-induced changes in the angle of peak torque can easily over- or underestimate the changes in peak torque when only one joint angle is tested (49,245). Baseline levels of force-generating capacity should be carefully established (≥ 1 familiarisation session), and muscle function should be monitored repeatedly (daily) until full recovery. Note, we advise caution about merely evaluating the immediate reductions in force-generating capacity (217), because this measurement may reflect muscle fatigue rather than muscle damage (88).

3. CYTOKINE RESPONSES TO EXERCISE-INDUCED MUSCLE DAMAGE

Researchers in exercise immunology have used various exercise protocols to investigate cytokine responses to muscle damage. These protocols include downhill running, eccentric actions of the leg or arm muscles, and traditional resistance exercise. Most studies have reported that these modes of exercise increase plasma

IL-6 concentration for several hours after exercise (see Table 3). Some studies have also reported that the plasma concentrations of interleukin-1 receptor antagonist (IL-1ra), monocyte chemotactic protein (MCP)-1 and granulocyte-colony stimulating factor (G-CSF) increase in the hours after exercise. Changes in the plasma concentrations of IL-8, IL-10, IL-12 and soluble tumor necrosis factor α receptor 1 (sTNF- α R1) are more variable. The plasma concentrations of IL-1 β , IL-2, IL-5, IL-13, IL-15, IL-17, TNF- α , leukemia inhibitory factor (LIF) and interferon (IFN)- γ do not change at all following exercise. In skeletal muscle, following resistance exercise, mRNA expression of IL-1 β , IL-6, IL-8 and TNF- α increases for up to 24 hours after exercise (see Table 4). IL-6, IL-8 and MCP-1 mRNA expression also increases for several hours after downhill running and eccentric actions of the quadriceps. Changes in IL-10 mRNA are more variable, while IL-2, IL-5 and IL-12 mRNA expression does not change after exercise. No research to date has investigated alterations in the anti-inflammatory cytokines IL-4 and IL-13 in skeletal muscle following acute exercise.

Table 3. Summary of systemic cytokine responses to eccentric and resistance exercise.

Reference	Exercise mode	Immediately post-exercise	1–4 h after exercise	4–24 h after exercise	≥ 24 h after exercise
(145,235,236, 239,277,294)	Downhill running	↑ IL-1ra, IL-6, IL-8, G-CSF, MCP-1	↑ IL-1ra, IL-6, IL-12p40, MCP-1 ↓ IL-8	↑ IL-6, IL-7, IL-8, IL-10, MCP-1, MIP-1 β	↑ IL-1ra ↓ IL-8 ↔ IL-6, G-CSF
		↔ IL-10, IL-12p40	↔ IL-10	↔ IL-2, IL-4, IL-5, IL-12p70, IL-13, IL-17, IFN- γ , IL-1 β , TNF- α , G-CSF	
(43,297)	Eccentric cycling	↑ IL-1ra, IL-6, sTNF- α R1	↑ IL-1ra, IL-6, sTNF- α R1		↑ IL-1ra, IL-6, sTNF- α R1 ↔ TNF- α
(77,228,256,322)	Eccentric exercise of the quadriceps	↔ TNF- α ↑ IL-6, MCP-1, G-CSF, M-CSF	↔ TNF- α ↑ IL-6, MCP-1, G-CSF ↔ IL-1ra, IL-8, IL-10, TNF- α , G-CSF, M-CSF, sTNF- α R1	↑ G-CSF ↔ IL-6, MCP-1, M-CSF	
(61,124,234,242)	Eccentric exercise of the elbow flexors	↑ IL-6 ↓ IL-8, IL-10 ↔ TNF- α , IL-1ra, IL-8, IL-10, G-CSF	↑ IL-6, IL-10, G-CSF, sTNF- α R1 ↓ IL-8 ↔ TNF- α , IL-1ra, IL-8, IL-10	↑ G-CSF, IL-10 ↓ IL-8 ↔ IL-1ra, IL-6, IL-8, IL-10, TNF- α , sTNF- α R1	↑ IL-6, IL-10, G-CSF ↓ IL-8, TNF- α ↔ IL-1ra, IL-6, IL-8, IL-10, TNF- α , sTNF- α R1
(35,36,214,215,276,305)	Resistance exercise	↑ IL-6, IL-8, IL-10 ↔ IL-6, IL-10, IL-15, TNF- α , LIF	↑ IL-6, IL-8, IL-10 ↔ IL-6, IL-10, TNF- α	↓ IL-1 β ↔ IL-15	↓ IL-1 β ↔ IL-6, IL-10, IL-15, TNF- α

Table 4. Summary of intramuscular cytokine mRNA responses to eccentric and resistance exercise.

Reference	Exercise mode	Cytokine	1–4 h after exercise	4–24 h after exercise	≥ 24 h after exercise
(36,45,80,139,165,215,246,253,303)	Resistance exercise	IL-1β	↑	↑	↑
		IL-2	↔		
		IL-5	↔		
		IL-6	↑	↑	↔
		IL-8	↑	↑	
		IL-10			↑
		IL-15	↔	↑	↔
		TNF-α	↑, ↔	↑	↔
		LIF		↑	
(45,116)	Downhill running	IL-1β	↔	↔	↔
		IL-6	↑	↑	↑
		IL-8	↑	↔	
		TNF-α	↔	↔	↑
		TGF-β			↑
(59,129,177,203,256)	Eccentric exercise of the quadriceps	IL-1β	↑		↑
		IL-6	↑		
		IL-8	↑		↔
		MCP-1	↑		↑
		TNF-α	↔	↑	↔
(172)	Electrical stimulation of gastrocnemius	IL-1β			↔
		TNF-α			↔
		MCP-1			↑

3.1 Cytokines as mediators of exercise-induced muscle damage

As described previously, exercise induces systemic and local cytokine responses in skeletal muscle. Over the past decade or so, considerable attention has focused on the biological role of cytokines derived from muscle (so-called ‘myokines’) in regulating metabolism in skeletal muscle and adipose tissue (237). Less is known concerning the role of cytokines in regulating inflammatory responses and adaptation to exercise-induced muscle damage. To examine whether cytokines are a cause or a by-product of exercise-induced muscle damage, a small number of studies have investigated the relationship between cytokine responses and markers of muscle damage. Three studies report that plasma cytokine concentrations correlate with plasma CK activity and myoglobin concentration after exercise (43,124,216). Other research has investigated the relationship between cytokines and muscle damage more directly by comparing cytokine responses to concentric versus eccentric actions, submaximal versus maximal eccentric actions and single versus repeated bouts of eccentric exercise.

3.1.1 Eccentric versus concentric muscle actions

Several studies have examined cytokine responses to eccentric exercise, which causes greater muscle damage than concentric exercise. Bruunsgaard *et al.* (43) demonstrated that serum IL-6 concentration and CK activity are higher after eccentric cycling compared with concentric cycling (Table 5; see addendum). Clarkson *et al.* (59,129) have also reported greater strength loss and gene expression of both IL-1R and MCP-1 after eccentric actions compared with concentric actions of the quadriceps. However, others have reported no differences in the plasma cytokine responses to level running versus downhill running, despite higher plasma CK activity and myoblobin concentration after downhill running

(235,236). Variation in exercise protocols, training status of study participants, and sampling times may account for some of these inconsistent findings.

3.1.2 Submaximal versus maximal eccentric exercise

As a variation to research comparing eccentric and concentric exercise, other studies have compared muscle damage and cytokine responses to submaximal and maximal eccentric exercise, which cause differing degrees of muscle damage. Malm *et al.* (181) observed that loss of strength was greater 1 d after downhill running at a gradient of 8° versus 4°, but they detected no changes in serum or muscle cytokines after either exercise trials. In another study, muscle damage (as demonstrated by loss of muscle strength) was greater after maximal versus submaximal eccentric actions of the elbow flexors, but cytokine responses were similar between the two trials (234).

3.1.3 Repeated bouts of eccentric exercise

Several studies have investigated whether adaptations to repeated bouts of eccentric exercise are associated with alterations in cytokine responses. However, this research has also produced equivocal findings (Table 5; see addendum). The results of two studies indicate less muscle damage, smaller changes in circulating IL-6, IL-8 and MCP-1, and greater changes in circulating IL-10 and macrophage inflammatory factor (MIF)-1 β in the days following two bouts of eccentric exercise (124,277). In contrast with these observations, other groups have found no difference in plasma IL-6 concentration following repeated bouts of eccentric actions of the knee extensors/flexors, despite evidence of less muscle damage (77,322). Once again, these discrepant findings may be due to differences in exercise protocols, training status of study participants, and sampling times. Two studies have reported that MCP-1 gene expression in *m. vastus lateralis* is higher following a repeated bout of eccentric actions (129), but lower after electrically-stimulated muscle actions (172) performed four weeks after an initial bout of the same exercise. As discussed previously, this discrepancy may reflect differences in the pattern of muscle fibre recruitment between voluntary and electrically-stimulated muscle actions.

3.2 Experimental considerations for examining the role of cytokines in muscle damage

Research to date has examined muscle cells and leucocytes as potential sources of cytokines during exercise; however, the dominant cellular source of circulating cytokines remains uncertain, for two main reasons. First, *in vitro* cell culture methods do not take into account the complex array of interactions between humoral factors produced by multiple organs during exercise. Although certain types of cells may generate large amounts of cytokines *in vitro*, cytokine synthesis *in vivo* may depend on the presence of other inhibitory (or stimulatory) factors in the local or systemic environment. Second, molecular analysis of isolated RNA or protein extracts is often performed using homogenised muscle, which makes it difficult to identify specific cell sources of cytokines.

To clarify the role of cytokines in muscle damage and adaptation in greater detail, more complex experimental procedures are required. Analysis of the circulating concentrations of cytokines is arguably insufficient to examine the role of

cytokines in muscle damage for two reasons. First, most cytokines are produced locally within skeletal muscle during exercise. Second, with the exception of IL-6, these cytokines are not released into the circulation (285). Regular muscle sampling in the first few hours and days after exercise provides the most direct evidence as to whether cytokines regulate muscle damage and regeneration. However, due to the invasive nature of muscle biopsies, most studies to date have collected no more than four biopsy samples at various time points after exercise. Variation in the time points for muscle sampling, coupled with different exercise protocols, makes it difficult to obtain a clear understanding of the time course of inflammatory responses to exercise-induced muscle damage. As discussed previously, some researchers have also questioned whether the biopsy procedure itself causes more inflammation than exercise (180,181).

Another alternative approach is to modulate or block cytokine activity prior to muscle damage, and then examine subsequent muscle regeneration. These procedures are obviously difficult to implement in human studies. Several studies have examined muscle regeneration following freeze injury in mice lacking cytokine activity. Compared with wild-type mice, recovery of muscular isometric strength is lower between 7–28 days post-injury in *CCR2^{-/-}* mice (314), at 12 days post-injury in mice depleted of TNF- α or its receptors (313), and at 14 days post-injury in *MCP^{-/-}* mice (317). These findings indicate that rather than causing muscle damage, cytokines such as TNF- α and MCP-1 and their receptors are required for successful muscle regeneration to occur. Conversely, whether over-expression of these cytokines and their receptors increases muscle injury is currently unknown. MCP-1 deficiency causes more rapid recruitment and activation of neutrophils (through increased expression of neutrophil chemoattractants) and delays recruitment of macrophages in injured muscle tissue. These effects delay the formation of new muscle fibres and increase lipid accumulation and necrosis in regenerating muscle tissue (270,317). The mechanisms through which TNF- α deficiency impairs muscle regeneration are less clear, but may also involve a decline in infiltrating neutrophils and macrophages (240) and/or the expression of myogenic regulatory factors (313). In contrast with TNF- α and MCP-1, IL-6 deficiency does not appear to alter muscle regeneration, even though IL-6 expression in muscle increases following injury (313) and IL-6 regulates the proliferation and differentiation of myoblasts (17,267). Taken together, these findings do not necessarily exclude IL-6 as a regulatory factor in muscle regeneration, but suggest that other factors such as TNF- α and MCP-1 and their receptors play more important roles. Few studies have reported any change in TNF- α mRNA expression in muscle after exercise, so its role in human skeletal muscle remains uncertain. IL-6 may be more active in regenerating tendon tissue (8). The research described above implicates TNF- α and MCP-1 and their receptors in muscle regeneration following acute muscle injury. They may play a different—and potentially negative—role in chronic diseases that involve muscle wasting.

Summary

In comparison with cellular inflammatory responses to exercise-induced muscle damage, much less is known about changes in local cytokine responses and their functional significance. Most studies have only collected muscle biopsies at one or two time points after exercise, which precludes any detailed assessment of the

role of cytokines during different phases of muscle inflammation and regeneration. Definitive evidence exists that muscle cells produce a variety of cytokines and chemokines *in vitro*, whereas it is more likely that various cell types synthesise cytokines in muscle following exercise. The results of studies that have used freeze or crush injury in animal muscle to investigate the role of cytokines are not necessarily applicable to humans, because this type of injury is generally more severe and localised than exercise-induced muscle damage. Although cytokines and chemokines regulate a variety of metabolic, endocrine and immunological functions, it remains unclear whether they are a cause or by-product of exercise-induced muscle damage. Until we gather more precise information about their functional role in exercise-induced muscle damage, there seems little rationale for athletes to attempt to attenuate cytokine responses to exercise through nutritional or pharmacological means.

4. SATELLITE CELL RESPONSE TO ECCENTRIC EXERCISE

Muscle cells are multi-nucleated, and can be five orders of magnitude larger than mononucleated cells (44,114). Because adult muscle nuclei (myonuclei) do not divide, new myonuclei must come from other sources when required. Satellite cells serve this role as so-called stem cells of skeletal muscle or myogenic precursor cells during both skeletal muscle adaptation and regeneration (55,118). During muscle hypertrophy, the growing myofibre may require additional myonuclei, because the area of the cytoplasm that each myonucleus can control is traditionally regarded as fairly constant (6,278). However, hypertrophy can proceed without satellite cell activity, probably because existing myonuclei are able to control larger areas of cytoplasm when stimulated (28,190,191).

Satellite cells are situated beneath the basal lamina, but in contrast to regular myonuclei, they are located outside the plasma membrane (sarcolemma). In response to an appropriate stimulus, satellite cells are activated, and then proliferate. Some activated satellite cells help to replenish the satellite cell pool. Other satellite cells migrate to areas where they differentiate and fuse with existing myofibres or produce new fibres. Exercise can stimulate satellite cells to re-enter the cell cycle and proliferate, as shown in several human training studies lasting 2–3 months (see summary in (174)). Interestingly, satellite cells may become activated and proliferate after a single bout of exercise that induces neither hypertrophy nor damage to myofibres (71,72,174,202). In this situation, although the satellite cells are activated, they do not necessarily fuse with myofibres to become myonuclei (no increase in number of myonuclei) or accumulate to generate new myofibres. This ‘low threshold’ activation of satellite cells may primarily serve to replenish the satellite cell pool, because a reduced satellite cell pool would diminish the regeneration potential of the muscle (261).

4.1 Satellite cell response to a single bout of eccentric exercise

Human studies investigating the skeletal muscle satellite cell responses to a single bout of eccentric exercise are summarised in Table 6. Figure 3 demonstrates the quantitative satellite cell responses in these studies. The proportion of satellite cells increases quickly within the first 24 hours after exercise and may remain elevated for 8 days or more.

Table 6: Human studies investigating the satellite cell (SC) response to a single bout of eccentric exercise in young, healthy subjects.

Reference	Exercise mode (thigh muscle if not indicated)	Subjects' training status	Sampling time points	Measure of SC given:	Context and comments
Crameri <i>et al.</i> (72)	Eccentric exercise: 50 one-leg 'drop down' jumps 8x10 reps at 30°/s 8x10 reps at 180°/s	Sedentary	2 d 4 d 8 d	NCAM % MN	First study to show increased SC number with single bout of exercise
Dreyer <i>et al.</i> (84)	Max eccentric: 6x16 reps at 60°/s	No resistance training	1 d	NCAM % MN /fibre	Larger SC response in younger than in older subjects
Crameri <i>et al.</i> (71)	Max eccentric: 10x10 reps at 30°/s 11x10 reps at 180°/s	No regular training	4 d 8 d	NCAM, Pax7 % MN	Larger response with electrical stimulation. No baseline data given
O'Reilly <i>et al.</i> (225)	Max eccentric: 30x10 reps 180°/s	No resistance training	4 h 1 d 3 d 5 d	NCAM % MN, /fibre	Association with HGF response
McKay <i>et al.</i> (196)	Max eccentric: 3.14 rad/s 30 x 10 reps	No resistance training	4 h 1 d 3 d 5 d	Pax7 % MN	Association with IL-6 signalling
Mikkelsen <i>et al.</i> (202)	Max eccentric: 10x10 reps at 30°/s 10x10 reps at 120°/s	Well trained	5 h 28 h 8 d	NCAM, Pax7 % MN, /fibre	SC response reduced by NSAID infusion
McKay <i>et al.</i> (197)	Max eccentric: 3.14 rad/s 30 x 10 reps	No resistance training	1 d	NCAM, Pax7 % MN, /fibre	Compared with FACS, similar results
Paulsen <i>et al.</i> (230)	Max eccentric (elbow flexors): 14x5 reps at 30°/s	Physically active	1 h – 7 d (combined)	NCAM % MN, /fibre	Biopsies from m. biceps brachii

NB: To quantify satellite cells, the number of positive cells is expressed relative to fibre number (per fibre) or as a proportion of the total number of myonuclei (MN), the latter calculated as $(\text{NCAM}+ \text{cells} / [\text{myonuclei} + \text{NCAM}+ \text{cells}] \times 100)$ or $(\text{Pax7}+ \text{cells} / [\text{myonuclei} + \text{Pax7}+ \text{cells}] \times 100)$.

In Figure 3, the relative satellite cell responses (normalised to pre-exercise values) observed in the studies from Table 6 are shown together. This figure shows that the observed responses are highly variable, even at similar time points and despite similarities between the exercise protocols. The satellite cell response does not appear to correlate with the stress and damage to the exercised muscle. For example, the study that reported the most damage after exercise (230) also reported the smallest increase in the number of satellite cells. When gross muscle damage does occur—as demonstrated in Paulsen *et al.* (230) and Crameri *et al.* (71)—the satellite cells leave their location and migrate as myoblasts to areas of need for regeneration (136,266). Note, however that in humans, the signs of severe damage and necrosis are first observed after about 4 days (71,137,230), while a strong satellite cell response is evident after only 24 hours (Figure 3). Further research is warranted to clarify the function and time course of changes in satellite cell activity in response to exercise-induced muscle damage.

4.1.1 Satellite cell identification

Satellite cells were first identified in 1961 using electron microscopy (185). Today, specific antibodies are generally used to identify and quantify satellite cells. Most human studies have used an antibody against NCAM (also known as CD56 and Leu19 (266)) to identify satellite cells (see Table 6). Because NCAM is a cell surface glycoprotein expressed on the membrane of satellite cells, this anti-

body marks the outer border of satellite cells. The transcription factor Pax7 is traditionally used to identify satellite cells in cell culture. Pax7 is a transcription factor that is expressed in the nuclei of satellite cells; thus, Pax7 antibodies only label the nucleus of the satellite cell. Lindström and Thornell (163) reported that 94% of all human satellite cells are both NCAM and Pax7 positive.

4.2 The role of the COX-pathway and NSAIDs in satellite cell activation signalling

Many factors are proposed to control satellite cell activity, yet the precise regulatory mechanisms in human skeletal muscle are not fully understood (9,30,327). Animal studies have identified several factors that influence satellite cells at different stages of their activity (for detailed reviews see (30,327)). Among these factors, the cyclooxygenase (COX) pathway is one of the most important (31,32,199). Non-steroidal anti-inflammatory drugs (NSAIDs) inhibit this pathway. In relation to muscle soreness and/or muscle damage, athletes often use NSAIDs, which highlights the importance of understanding their effect on muscle regeneration (7,91,328).

COX2 inhibitors and the non-selective NSAID ibuprofen reduce hypertrophy of mice and rat skeletal muscle (222,279). In humans, NSAIDs attenuate the satellite cell response to exercise (174,202), which is discussed in more detail below. How NSAIDs or prostaglandins exert their effect on satellite cells is not known.

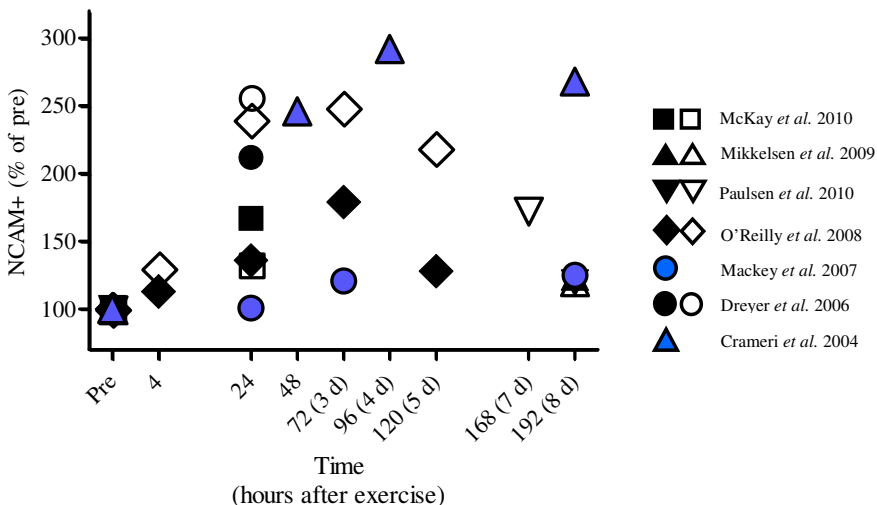


Figure 3: Satellite cell response to a single bout of maximal exercise. The satellite cells were identified by antibodies against NCAM on muscle cross sections from biopsies obtained at different timepoints after exercise. Eccentric exercise was used in all studies except from Mackey *et al.* 2007 (36 km run). Biopsies were obtained from *m. vastus lateralis* except from Paulsen *et al.* 2010 (*m. biceps brachii*). The number of NCAM+ cells is expressed as proportion of total myonuclei (filled symbols) or per muscle fibre (open symbols) and shown as percentage of pre-exercise values.

4.2.1 COX and prostaglandins

The primary function of the COX enzymes is to generate prostaglandins. Prostaglandins (e.g., PGE and PGF) are ubiquitous lipid compounds derived from membrane phospholipids. They regulate smooth muscle tissue, acting as vasodilators to enhance blood flow in a wide range of tissues including the kidneys. They also sensitise nociceptors (pain response), regulate inflammation and fever, and protect the mucus layer in the gastrointestinal tract (104). Among the various COX enzymes, COX1 and COX2 are the most common (83,104). COX1 is constitutively expressed in several cell types, and synthesises prostaglandins that are important for homeostasis. COX2 is induced during cell injury, inflammation and mechanical stretch, and it synthesised prostaglandins that mediate inflammation and pain. Traditional NSAIDs inhibit both COX1 and COX2 isoforms (120). COX2 selective inhibitors have been developed to reduce the adverse effects of traditional NSAIDs on the gastrointestinal tract and the kidneys, while maintaining their analgesic and anti-inflammatory effects (34,309).

4.2.2 COX expression and prostaglandin response to exercise in healthy human muscle

Several studies have investigated the expression of the different COX isoforms in human skeletal muscle, although mainly at the mRNA level. COX1 mRNA is highly expressed in human skeletal muscle (COX1v1 and COX1v2), but it does not respond to exercise or NSAIDs (47,203,318). By contrast, COX2 mRNA is expressed at very low levels at rest, and is either unchanged (47,203) or induced with exercise (45,46,318) and some NSAIDs (47,203). COX3, which constitutes three different splice variants of COX1, is also expressed at very low levels (318). COX1 protein expression remains unchanged with exercise and NSAID treatment (47). COX2 protein is less abundant in skeletal muscle. Immunohistochemical studies have identified both COX1 and COX2 in human skeletal muscle (288,293). However, it is uncertain whether the antibodies used in these studies are specific for the COX enzymes, particularly because COX2 protein expression in human skeletal muscle is very low (47,293). The level of prostaglandins in skeletal muscle increases with resistance exercise, as indicated by the presence of PGF_{2α} in muscle homogenate (300), and PGE₂ efflux from muscle using microdialysis (142). By contrast, PGE₂ does not seem to change following the first hours after eccentric exercise (230).

4.2.3 Effect of NSAIDs on healthy human muscle

4.2.3.1 Muscle function and DOMS following exercise

The effects of NSAIDs on DOMS and recovery of muscle function following exercise have been widely investigated during the last decades (see reviews (4,18,19)). Research on the use of NSAIDs to relieve DOMS has yielded conflicting results. Likewise, the evidence for the effects of NSAIDs on circulating CK activity is inconclusive. Considering the widespread use of NSAIDs among athletes (110,198,311), the effects of NSAIDs on adaptation to exercise training are important to consider. Whether short-term NSAID therapy affects muscle adaptation to training in humans is largely unknown. The discussion below focuses on healthy young humans, but this issue is just as relevant to the elderly and clinical patients who may consume NSAIDs regularly for medicinal purposes.

4.2.3.2 Cellular effects of NSAIDs on human muscle

The cellular effects of exercise combined with NSAIDs on skeletal muscle are not well known. Bourgeois *et al.* (33) demonstrated that consuming the NSAID naproxen for 48 hours following knee extensor exercise did not affect the number of total leucocytes in *m. vastus lateralis* (leucocyte common antigen, CD45+ cells). However, muscular strength returned to baseline more rapidly in response to naproxen compared with the placebo treatment. Treatment with the COX2 specific inhibitor diclofenac for a total of 27 days before and after 20 min step exercise reduced histological abnormalities in muscle (foci of inflammation or necrotic fibres), DOMS and plasma CK activity (224). Animal studies point to a negative effect on skeletal muscle regeneration and adaptation (31,152,204,222,279), whereas evidence from human studies is sparse.

Trappe *et al.* (301) reported that ingestion of ibuprofen for 24 hours following one session of intense eccentric exercise suppressed the increase in mixed muscle protein synthesis rates that normally occurs following exercise. The protein synthesis rate measured 24 hours after exercise, increased by 76% in the placebo group, whereas it remained unchanged in the ibuprofen group. Ibuprofen also suppressed the PGF_{2α} response to exercise (300). Mackey *et al.* (174) showed that ingestion of NSAIDs in humans attenuates the satellite cell response to endurance exercise. In this study, satellite cell number remained unchanged 8 days after a 36-km run in athletes who consumed NSAIDs after exercise. By contrast, satellite cell number was elevated by 27% 8 days after exercise in athletes who consumed placebo. This finding points towards a negative effect of NSAIDs on satellite cell proliferation *in vivo* in humans. This is consistent with reports from animal models that COX enzyme activity is necessary for satellite cell activity and muscle regeneration.

We have also shown that infusion of NSAIDs before, during and for 4.5 hours after eccentric exercise (a total of 7.5 hours) reduces the satellite cell proliferation observed 8 days after exercise (202). A moderate dose of ibuprofen (400 mg/d) during 6 weeks training does not, however, alter muscle hypertrophy, strength or soreness (149). The few human studies using COX2 specific inhibitors have not observed any effect on satellite cells (230) or mixed muscle protein synthesis (48). Burd *et al.* (48) administered celecoxib (600 mg) for 24 hours following a single session of heavy eccentric exercise. Treatment with celecoxib did not alter mixed muscle protein synthesis following exercise (0.06 to 0.11 %/h) compared with the placebo treatment (0.07 to 0.09 %/h). Following eccentric exercise of the elbow flexors, Paulsen *et al.* (230) observed that treatment with celecoxib (400 mg/d) for 7 days did not suppress the increase in numbers of satellite cells or inhibit myofibre regeneration after exercise, when compared to a placebo treated group.

Animal and cell culture studies mainly show that NSAIDs negatively affect satellite cells, hypertrophy and regeneration of skeletal muscle. Results from studies on young, healthy humans indicate either a negative effect (301) or no effect (203) of traditional NSAIDs on muscle protein synthesis (300). Two studies report negative effects of NSAIDs on satellite cells (174,202). Hypertrophy is not reduced following moderate (400 mg/day) doses of ibuprofen (149). Furthermore, COX2 specific inhibitors do not alter muscle protein synthesis (48) or satellite cells (230).

4.3 Inflammation in skeletal muscle: friend or foe?

Current evidence suggests that in healthy young individuals, reducing inflammation by use of NSAIDs may interfere with muscle regeneration or hypertrophy. In contrast, NSAIDs may be beneficial under conditions of excessive or prolonged inflammation. For example, in the elderly, low-grade systemic inflammation may contribute to the loss of muscle mass (termed 'sarcopenia'). In this context, NSAIDs may benefit maintenance of muscle mass (254). Low-grade systemic inflammation that accompanies ageing has attracted a lot of attention during recent years. Levels of inflammatory markers, such as IL-6 and CRP increase slightly with ageing, and these higher levels are correlated with disability and mortality in humans (23,117,231). During 12 weeks of resistance training in elderly people, ibuprofen (3×400 mg/day) promoted gains in quadriceps muscle volume and strength (299).

In many chronic disease states, systemic inflammation may contribute to loss of muscle mass (termed 'cachexia'). In animal models of diseases like cancer (125,189) and arthritis (111), NSAIDs help to maintain muscle mass. In these studies, indomethacin (inhibiting COX1 and COX2) and COX2 specific NSAIDs reduce the negative effects of arthritis on body mass, muscle mass and muscle gene expression. Similarly, ibuprofen and indomethacin help to preserve muscle mass in tumor-bearing mice with reduced muscle mass (189).

Summary

Satellite cells are necessary to repair muscle damage. Animal studies show that the COX pathway is essential for this, and that NSAIDs inhibit repair and regeneration. Likewise, in healthy young humans, NSAIDs seem to reduce the capacity to repair muscle damage, since the number of satellite cells is reduced. The biological significance of these findings is that consumption of NSAIDs to alleviate soreness and expedite muscle repair after damage may be contraindicated. Inflammation (or at least a functional COX-pathway) may be necessary for muscle adaptation and regeneration in young, healthy people. Consequently, inhibiting inflammation using NSAIDs may have negative effects on skeletal muscle. Evidence from human studies indicates that consumption of large doses of traditional NSAIDs may negatively affect skeletal muscle in healthy young humans, whereas moderate doses of NSAIDs or COX2 selective inhibitors have apparently no effect. Contrary to this, inhibition of inflammation using NSAIDs may be beneficial in elderly or in individuals with chronic diseases that cause muscle atrophy. The recommendations on use of NSAIDs are therefore likely to differ between subjects, and it seems important to consider health, age and training status of individuals when considering the use of NSAIDs.

CONCLUSIONS

Currently there is no common definition or accepted way to measure the degree of exercise-induced muscle damage. However, both animal and human studies have repeatedly demonstrated that severe exercise-induced muscle damage encompasses myofibrillar disruptions, local inflammation with leucocyte accumulation, segmental myofibre necrosis, and subsequent regeneration involving satellite cell

activation. In humans, the extent of damage and inflammation varies considerably, in contrast to more consistent findings in animal models. There is reasonably solid evidence that unaccustomed, isolated, maximal eccentric actions over large range of motion are necessary to inflict severe exercise-induced damage, including necrosis. Still, some subjects do not display severe damage even after such 'extreme' protocols. Exercise protocols that are closer to exercise used in regular athletic training (e.g., traditional resistance exercise) generally cause minor damage, although some myofibrillar disturbances seem to occur to some degree. Irrespective of the exercise protocol, changes in muscle function (force-generating capacity) seem to be the best marker for the overall level of damage. Thus, if the reduction in muscle force-generating capacity is less than 20% after exercise and recovery is complete in the following 48 hours, the degree of damage is likely to be minor and signs of classical inflammation (i.e., leucocyte accumulation in the muscle tissue) are hardly detectable or absent. Nevertheless, local cytokine production may still occur. By contrast, reductions of muscle force-generating capacity that surpass 50% and prolonged recovery requiring more than one week, indicate severe exercise-induced muscle damage. Consequently, we recommend that investigations of exercise-induced muscle damage should always monitor muscle function until full recovery.

The cytokine response to exercise seems robust, but complex. The circulating concentrations of various cytokines increase during and after exercise, yet the cellular sources of these cytokines are difficult to ascertain. Myofibres have the potential to produce cytokines, but with the exception of IL-6, there is no evidence that other cytokines are released from skeletal muscle into the circulation during exercise. Leucocytes also seem an unlikely major source of circulating cytokines following exercise-induced muscle damage. In the exercised muscles, the increased mRNA expression of cytokines is poorly supported with evidence of increased protein expression. One exception is MCP-1, but this chemokine appears to be produced by stromal cells (macrophages) and satellite cells, rather than by myofibres. Most evidence indicates that the cytokine response to exercise is not necessarily an acute inflammatory response to muscle damage. Instead, cytokines may play a greater role in mediating glucose metabolism and muscle regeneration.

Satellite cells are activated by various types of exercise, both damaging and apparently non-damaging exercise. Thus, the threshold for satellite cell activation is rather low, and the satellite cell response does not seem to be directly related to muscle damage markers. However, only if the initial muscle damage induces a necrotic process in segments of myofibres will the satellite cells leave their position and migrate to the area of damage as (differentiated) myoblasts. The COX pathway by which prostaglandins are synthesised is associated with the satellite cell response, because blocking this pathway in animals reduces the regeneration and growth of skeletal muscle. Although COX2 is essential in animal muscles, selective COX2 inhibitors do not always inhibit muscle regeneration in humans. This could be linked to the fact that both the mRNA and protein levels of COX2 are very low in human skeletal muscle. Non-selective NSAIDs (blocking both COX1 and COX2) can inhibit satellite cells and may affect muscle regeneration and adaptation in young healthy individuals; yet when combined with resistance training, NSAID supplementation facilitate muscle hypertrophy in elderly people.

ADDENDUM

Table 1A: Human studies that have investigated the presence of inflammatory cells (leucocytes) in biopsy samples obtained after types of exercise that apparently inflicted 'mild' exercise-induced muscle damage. In studies with treatment groups, data from the control/placebo group are presented.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes	Acute ↓ in muscle function	Recovery of muscle function	Myofibrillar disruptions	Signs of necrosis	Peak CK (IU·L ⁻¹)
			Group response	Individual response					
Bourgeois <i>et al.</i> (33)	Resistance exercise (concentric/eccentric): Leg press and knee-extension (single leg), 6 x 10 repetitions; 80–85% of 1 RM.	VL: 1 d	1 d (contra-lateral leg)	No	~9% at 1 d	~3% below baseline 2 d after exercise	NA	NA	~750 (1 d)
Féasson <i>et al.</i> (90)	30 min downhill running at 12° (~11 km·h ⁻¹ ; ~54% of VO _{2max})	VL: 0 h and 1 and 14 d	Pre	No	~15% (max power during cycling)	Within 7 d (no tests between day 1 and 7)	Yes	No	~1000 (1 d)
Malm <i>et al.</i> (181)	45 min downhill running at either 4° (50% of VO _{2max}) or 8° (max tolerated speed)	VL: 2 d	Control group	No	≤15% (isometric; 1 d; at 8°)	Within 2 d	NA	No	~1000 (1 d; at 8°)
Cramer <i>et al.</i> (71)	210 max eccentric actions using the knee-extensors in one randomly chosen leg. The exercise had two phases: 100 actions at 30°·s ⁻¹ and 110 actions at 180°·s ⁻¹ ROM: 10–90°.	VL: 5 h, 1, 4 and 8 d	Pre	Yes (CD68)	~16% (isometric)	Within 2 d	Yes	No	NA

Abbreviations: 0° = extended joint; 0 h, immediately after exercise; BB, m biceps brachii; DOMS, delayed onset muscle soreness; EM, electron microscopy; LCA, leucocyte common antigen; MC, mononuclear cells; MPO, myeloperoxidase; NA, not analysed/assessed; VL, m. vastus lateralis; Sol, m. soleus; Gast, m. gastrocnemius; PL, m. peroneus longus; TA, m. tibialis anterior.

Table 1B: Human studies that have investigated the presence of inflammatory cells (leucocytes) in biopsy samples obtained after types exercise that apparently inflicted 'moderate' exercise-induced muscle damage. In studies with treatment groups, data from the control/placebo group are presented. See Table 1A for abbreviations.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes		Acute ↓ in muscle function	Recovery of muscle function	Myofibrillar disruptions	Signs of necrosis	Peak CK (IU·L ⁻¹)
				Group response	Individual response					
Fridén <i>et al.</i> (103)	Eccentric cycling exercise for 30 min at an intensity corresponding to 80-100% of VO _{2max} during concentric cycling	VL: 0 h and 3 and 6 d	Pre	No	?	~24% (isometric)	Within 6 d	Yes	No	NA
Crenshaw <i>et al.</i> (75,76)	Max eccentric actions (60°·s ⁻¹) with the knee-extensors in one leg until exhaustion; the other (randomly chosen) leg performed concentric work. ROM: 30-120°.	VL: 2 d	2 d ('concentric leg')	No	?	NA	~20% below baseline 2 d after exercise (isometric/concentric)	Yes	No	NA
Stupka <i>et al.</i> (287)	36 eccentric actions of leg press and 100 isolated eccentric actions at 120% of max concentric strength, using the knee-extensors in one leg. ROM: 15-90° (both exercises). The weakest leg evaluated from a pre-test) was exercised. 240 max eccentric actions (30°·s ⁻¹) using the knee-extensors in one leg. ROM: 50-110°.	VL: 1 d	1 d (contralateral leg)	Yes (CD68)	-	~31% (concentric)	Within 7 d	Yes	NA	♀: 200-1400, ♂: 300-2100 (range; 4 d)
Beaton <i>et al.</i> (24)	36 eccentric actions (30°·s ⁻¹) using the knee-extensors in one leg. ROM: 50-110°.	VL: 1 d	1 d (contralateral leg)	Yes (CD68; no MPO)	-	~50% (concentric/isometric)	Within 4 d	Yes	No	120-1300 (range; 3 d)

Table 1B: Human studies that have investigated the presence of inflammatory cells (leucocytes) in biopsy samples obtained after types exercise that apparently inflicted 'moderate' exercise-induced muscle damage. In studies with treatment groups, data from the control/placebo group are presented. See Table 1A for abbreviations.

Study	Exercise	Muscle biopsy	Control biopsy	Group		Individual				Peak CK (IU·L ⁻¹)
				Leucocytes		Acute ↓ in muscle function	Recovery of muscle function	Myofibrillar disruptions	Signs of necrosis	
Beaton <i>et al.</i> (25)	300 max eccentric actions (30°·s ⁻¹) using the knee-extensors in one randomly chosen leg. ROM: 60-120°.	VL: 4 h and 1 d	Pre	Yes (CD68; no MPO and elastase)	-	~54% (isometric)	Within 7 d	Yes	NA (reduced desmin and dystropin staining)	~300 (2 d)
	300 eccentric and concentric actions. The subjects rose from a chair with one randomly chosen leg and lowered the body weight back to a seating position with the other leg (20 cm hip displacement).									
Hubal <i>et al.</i> (129)		VL: 6 h	6 h ('concentric leg')	Yes (MAC387)	-	~32% (isometric)	~23% below baseline 5 d after exercise	NA	NA	NA
Mikkelsen <i>et al.</i> (202)	200 max eccentric actions using one leg (knee-extensors); both legs were exercised. The exercise had two phases: 100 actions at 30°·s ⁻¹ and 100 actions at 120°·s ⁻¹ . ROM: 10-90°.									
		VL: 8 d	Pre	No	Yes, 2 of 8 subjects (CD16 and CD68)	~28% (isometric)	Within 8 d	NA	No	~1000 (1 d)
Paulsen <i>et al.</i> (229)	300 max eccentric actions using the knee-extensors in one randomly chosen leg. ROM: 30-110°.	VL: 30 min, 4 and 8 h and 1, 4 and 7 d	VL: 30 min, 4 and 8 h and 1, 4 and 7 d	Yes (CD16, CD68)	-	~47% (concentric)	Within 7 d	Yes	Yes (~1%)	~200-2500 (range; 4 d)

Table 1C: Human studies that have investigated the presence of inflammatory cells (leucocytes) in biopsy samples obtained after types of exercise that apparently inflicted 'severe' exercise-induced muscle damage. In studies with treatment groups, data from the control/placebo group are presented. See Table 1A for abbreviations.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes	Acute ↓ in muscle function	Recovery of muscle function	Myofibrillar disruptions	Signs of necrosis	Peak CK (IU·L ⁻¹)
				Group response	Individual response				
Hikida <i>et al.</i> (121,269)	Marathon (running)	Gast: 0 h and 1, 3, 5, and 7 d	Pre	Yes (EM)	-	~47% (concentric)	Yes	Yes	NA
	1) Eccentric exercise using the elbow flexors until 50% loss of force								
Jones <i>et al.</i> (137,257)	2) Backwards downhill walking (large strain on the calf muscles)	BB and Sol/Gast: 4, 5, 7, 8, 9, 10, 12, 14 and 20 d	No	Yes (MC)	-	>50% (eccentric)	NA	Yes	~750-80000 (range; 4-6 d)
	70 max eccentric actions (100°·s ⁻¹) with the knee- extensors in one randomly chosen leg. ROM: almost full extension to almost full flexion (subjects in prone position).								
Child <i>et al.</i> (60)		VL: 4 and 7 d	Pre (randomly selected)	Yes (MC)	-	~50% (isometric)	NA	Yes	~16000 (4 d)
	Max eccentric cycling exercise; 5 x 5 min								
Hellsten <i>et al.</i> (119)		VL: 45 min, 1, 2 and 4 d	Pre, 45 min and 2 d	Yes (CD11b)	-	~54% (isometric)	NA	NA	~13300 (4 d)
	70 max eccentric actions using the elbow flexors in one randomly chosen arm. ROM: 145-5°.								
Paulsen <i>et al.</i> (154,230)		BB: 1 h and 2, 4 and 7 d	BB: 1 h and 2, 4 and 7 d	Yes (CD68, EM)	-	~50% (isometric)	Yes	Yes	~300-25000 (range; 4 d)

Table 2A: Studies in which *no inflammatory cells (leucocytes) were found* after voluntary exercise in humans. Muscle function was not assessed. In studies with treatment groups, data from the control/placebo group is presented. See Table 1A for abbreviations.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes		Myofibrillar disruptions	Signs of necrosis	Peak CK (IU·L ⁻¹)
				Group response	Individual response			
Fridén <i>et al.</i> (102)	Running down stairs: 10 x 10th floor to ground floor.	Sol: 2 and 7 d	Pre	No	?	Yes	No	NA
Kuipers <i>et al.</i> (150)	30, 45 or 60 min of eccentric cycling exercise at ~80% $\dot{V}O_{2max}$	VL: 0 h and 1 d	Pre	No	Yes, in two subjects exercising for 45 and 60 min	No	NA	< 200 (unchanged)
Warhol <i>et al.</i> (310)	Marathon (running)	Gast: Some hours, 1, 2, 3, 5, 7, and 10 d and 2, 3, 4, 6, 8, 10 and 12 weeks	Control group	No	?	Yes	No	NA
Nurenberg <i>et al.</i> (223)	30 min downhill running at 8°; 8 km·h ⁻¹	Sol, Gast, TA, PL: 2 d	No	No	?	Yes	No	200-1200 (range; 12-36 h)
Malm <i>et al.</i> (180)	Eccentric cycling exercise for 30 min at an intensity corresponding to 80-100% of $\dot{V}O_{2max}$ during concentric cycling (250-300 W).	VL: 0 and 6 h and 1, 2, 4 and 7 d	Pre and control group	No	?	NA	No	~120 (1 d)
Yu <i>et al.</i> (324-326)	1) Running down stairs: 15 x 10th floor to ground floor; 2) Eccentric cycling exercise; 3) Downhill running (8°)	Sol: 1 h, 2-3 and 7-8 d	Control group	No	?	Yes	No	< 1000
Cramer <i>et al.</i> (72,73)	50 one-leg drop down jumps (45 cm) followed by 80 eccentric actions at 30°·s ⁻¹ and 80 eccentric actions at 180°·s ⁻¹ .	0, 2, 4 and 8 d	Contra-lateral leg	No	Yes (CD68; 1 of 8 subjects)	NA	No (1 of 8 subjects)	NA

Dennis <i>et al.</i> (81)	Resistance exercise (concentric/eccentric): Leg press and knee-extension (both legs): 4 x 8 reps (to failure in the 4th set) at 80% of 1 RM.	VL: 1 and 3 d	Pre	No	Yes (individual changes were found)	NA	NA	NA
Przybyla <i>et al.</i> (246)	Resistance exercise (concentric/eccentric): Leg press and knee-extension (both legs): 4 x 8 reps (to failure in the 4th set) at 80% of 1 RM.	VL: 3 d	Pre	No	?	NA	NA	NA

Table 2B: Studies in which *inflammatory cells (leucocytes)* were found after voluntary exercise in humans. Muscle function was not assessed. See Table 1A for abbreviations.

Study	Exercise	Muscle biopsy	Control biopsy	Leucocytes		Myofibrillar disruptions	Signs of necrosis	Peak CK (IU·L ⁻¹)
				Group response	Individual response			
O'Reilly <i>et al.</i> (226)	Eccentric cycling for 45 min (3 x 15 min) at 70-90% of VO _{2max} (~180-220 W)	VL: 0 h and 10 d	Pre	Yes (EM)	-	Yes	Yes	NA
Costill <i>et al.</i> (70)	Eccentric actions using the knee-extensors in one leg; 10 x 10 repetitions with 120% of 1 RM. 30 min after the eccentric exercise the subjects performed a cycling exercise to deplete their glycogen stores (both legs).	VL: 1.5 h and 1 and 3 d	1.5 h and 1 and 3 d (contralateral leg)	Yes (MC)	-	NA	NA	~7000 (3 d)
Staubert <i>et al.</i> (283)	70 max eccentric action (120°-1) using the elbow flexors in the non-dominant arm. ROM: 120°.	BB: 2 d	2 d (contralateral arm)	Yes (MC)	-	NA	Yes (~2%)	NA
Widrick <i>et al.</i> (320)	Eccentric actions using the knee-extensors in one leg; sets of 6 repetitions until failure with 120% of 1 RM. Subjects had the evening before performed a cycling exercise to deplete their glycogen stores (both legs).	VL: 0 and 6 h and 1 and 3 d	0, 6 h and 1 and 3 d (contralateral leg)	Yes (MC)	-	NA	Yes	< 300 (unchanged)
Crenshaw <i>et al.</i> (74)	Ultramarathon footrace (160 km)	Gast: 1 d	No	Yes (EM)	-	Yes	Yes (~1%)	NA

Fielding <i>et al.</i> (92)	45 min downhill running at 16°; 75% max heart rate.	VL: 45 min and 5 d	Pre	Yes (neutrophils)	-	Yes	NA	~300 (1 d)
O'Grady <i>et al.</i> (224)	20 min eccentric stepping exercise; step height was 110% of the lower leg length.	VL: 12 d (right leg)	Pre (left leg)	Yes (MC)	-	NA	Yes	~1800 (3 d)
Stupka <i>et al.</i> (286)	Eccentric actions using the knee-extensors in one leg; leg press 3x12 and knee-extension 9x12 at 120% of 1 RM.	VL: 2 d	VL: 2 d	Yes (LCA; increase only in males)	-	Yes	No	♀: ~600 ♂: ~1000 (6 d)
Peterson <i>et al.</i> (241); Trappe <i>et al.</i> (302)	10-14 sets of 10 actions with the knee-extensors in the non-dominant leg. Load: 120% of max concentric strength. ROM: 0-90°.	VL: 1 d	Pre (contra-lateral leg)	Yes (CD68, not CD15)	-	NA	NA	~2250 (5 d)
Mahoney <i>et al.</i> (177)	300 max eccentric actions (120°·s ⁻¹) using the knee-extensors in the non-dominant leg. ROM: 30-90°.	VL: 3 h and 2 d	Pre	Yes (CD68, MPO)	-	Yes	NA	~300 (2 d)
MacNiel <i>et al.</i> (175)	150 max eccentric actions (120°·s ⁻¹) using the knee-extensors in the right leg. ROM: 30-90°.	VL: 3 h and 2 d	Pre (left leg)	Yes (CD68, MPO)	-	NA	NA	~500 (2 d)

Table 5. Summary of changes in cytokines and markers of muscle damage after exercise.

Reference	Exercise mode	Cytokine	Time of peak Δ	Function	Time of peak Δ	Protein	Time of peak Δ
Buford <i>et al.</i> (45)	Downhill running	IL-6 mRNA IL-8 mRNA	6% $\uparrow$, 3 h 8% $\uparrow$, 3 h			Serum CK	6x $\uparrow$, 1 d
Kingsley <i>et al.</i> (145)	Downhill running	Serum IL-6	1.2x $\uparrow$, 0 h			Plasma CK Plasma Mb	2x $\uparrow$, 1 d 80% $\uparrow$, 0 h
Malm <i>et al.</i> (181)	Downhill running 4° gradient	IL-6, LIF protein in muscle	No change	Strength ^b Soreness ^b	No change 2, 0 h	Serum CK	70% $\uparrow$, 1 d
	8° gradient	IL-6, LIF protein in muscle	No change	Strength ^b Soreness ^b	15% $\downarrow$, 1 d 3, 0 h	Serum CK	4.6x $\uparrow$, 4 d
Malm <i>et al.</i> (180)	Eccentric cycling	IL-1 β protein in muscle	60% $\uparrow$, 0 h			Plasma CK	1.2x $\uparrow$, 1 d
Chen <i>et al.</i> (59)	Eccentric contractions of the quadriceps	MCP-1 mRNA	25x $\uparrow$, 4–8 h	Strength	9% $\downarrow$, 3 d		
Ross <i>et al.</i> (256)	Eccentric contractions of the quadriceps	MCP-1 mRNA IL-6 mRNA IL-8 mRNA	1.3x $\uparrow$, 3 h 70% $\uparrow$, 3 h 1.2x $\uparrow$, 3 h			Serum Mb	2.3x $\uparrow$, 3 h
Paulsen <i>et al.</i> (228)	Eccentric contractions of the quadriceps	Plasma M-CSF Plasma IL-6 Plasma G-CSF Plasma MCP-1	50% $\uparrow$, 0 h 4x $\uparrow$, 6 h 70% $\uparrow$, 6 h 1.6x $\uparrow$, 6 h	Strength	34% $\downarrow$, 6 h 24% $\downarrow$, 4 d	Serum CK	50x $\uparrow$, 4 d
Childs <i>et al.</i> (61)	Eccentric contractions of the elbow flexors	Plasma IL-6	4x $\uparrow$, 2 d			Serum CK Serum Mb Serum LDH	20x $\uparrow$, 3 d 4x $\uparrow$, 2 d 5x $\uparrow$, 3 d
Phillips <i>et al.</i> (242)	Eccentric contractions of the elbow flexors	Serum IL-6	1.5x $\uparrow$, 1 h	Soreness ^a	35 mm	Serum CK	2.4x $\uparrow$, 3 d
Peake <i>et al.</i> (234)	Eccentric contractions of the elbow flexors Submaximal Maximal	Serum IL-6 Serum sTNF α R1 Serum IL-6 Serum sTNF α R1	80% $\uparrow$, 3 h 40% $\uparrow$, 3 h 40% $\uparrow$, 3 h 50% $\uparrow$, 3 h	Strength ^a Soreness ^a Strength ^a Soreness ^a	10% $\downarrow$, 1 d 15 mm, 2 d 40% $\downarrow$, 1 d 21 mm, 2 d	Plasma CK Plasma Mb Plasma CK Plasma Mb	2.4x $\uparrow$, 4 d 100% $\uparrow$, 3 h 1.3x $\uparrow$, 4 d 60% $\uparrow$, 3 h
Bruunsgaard <i>et al.</i> (43)	Concentric cycling Eccentric cycling	Serum IL-6 Serum IL-6	50% $\uparrow$, 2 h 4.5x $\uparrow$, 2 h			Serum CK Serum CK	No change 55x $\uparrow$, 4 d
Peake <i>et al.</i>	Level running	Plasma IL-6	4x $\uparrow$, 0 h			Plasma CK	20% $\uparrow$, 0 h

(233,235,236)

Downhill running

Plasma IL-1ra	1.3× ↑, 1 h	Plasma Mb	1.1× ↑, 1 h
Plasma IL-10	No change	Plasma CK	60% ↑, 0 h
Plasma IL-6	4.6× ↑, 0 h	Plasma Mb	18× ↑, 1 h
Plasma IL-1ra	2.4× ↑, 1 h		
Plasma IL-10	No change		

Groisser *et al.*
(77)Eccentric
contractions of the
quadriceps

Bout 1	7× ↑, 0.5 h	Serum Mb	290× ↑, 0.5 h
Bout 2	7× ↑, 0.5 h	Serum Mb	No change

Hirose *et al.*
(124)Eccentric
contractions of the
elbow flexors

Bout 1	60% ↑, 3 d	Strength	43% ↓, 2 d
Bout 2	25% ↑, 3 d	Soreness ^a	37 mm, 2 d
		Strength	19% ↓, 2 d
		Soreness ^a	20 mm, 2 d

Hubal *et al.*
(129)Contractions of the
quadriceps

Bout 1	9.2× higher (vs. concentric)	Strength	35% ↓, 3 d
Concentric	5× higher (vs. concentric)		
Eccentric			
Bout 2			
Concentric	0.7× higher (vs. Bout 1)	Strength	22% ↓, 3 d
Eccentric	1.1× higher (vs. Bout 1)		
	2.6× higher (vs. Bout 1)		
	1.9× higher (vs. Bout 1)		

Smith *et al.*
(277)

Downhill running

Bout 1	Serum IL-6	6 pg/mL, 12 h	Serum CK	~900 U/L, 1 d
	Serum IL-10	0.8 pg/mL, 12 h		
	Serum MCP-1	103 pg/mL, 12 h	Serum CK	~340 U/L, 1 d
Bout 2	Serum MIP-1β	42 pg/mL, 12 h		
	Serum IL-6	12 pg/mL, 12 h		
	Serum IL-10	1.6 pg/mL, 12 h		
	Serum MCP-1	93 pg/mL, 12 h		
	Serum MIP-1β	50 pg/mL, 12 h		

N.B. Only muscle function > 1 day post-exercise is reported because changes in strength < 1 day post-exercise most likely represent acute changes in muscle fatigue rather than damage *per se*. ^a Soreness was assessed using a visual analogue scale measured in millimeters (mm). ^b Soreness was assessed on a scale from 0–10.

REFERENCES

1. Abbott BC and Bigland B. The effects of force and speed changes on the rate of oxygen consumption during negative work. *J Physiol* 120: 319-325, 1953.
2. Abbott BC, Bigland B and Ritchie JM. The physiological cost of negative work. *J Physiol* 117: 380-390, 1952.
3. Abraham WM. Factors in delayed muscle soreness. *Med Sci Sports* 9: 11-20, 1977.
4. Alaranta A, Alaranta H and Helenius I. Use of prescription drugs in athletes. *Sports Med* 38: 449-463, 2008.
5. Allen DG. Eccentric muscle damage: mechanisms of early reduction of force. *Acta Physiol Scand* 171: 311-319, 2001.
6. Allen DL, Roy RR and Edgerton VR. Myonuclear domains in muscle adaptation and disease. *Muscle Nerve* 22: 1350-1360, 1999.
7. Almekinders LC. Anti-inflammatory treatment of muscular injuries in sport. An update of recent studies. *Sports Med* 28: 383-388, 1999.
8. Andersen MB, Pingel J, Kjaer M and Langberg H. Interleukin-6: a growth factor stimulating collagen synthesis in human tendon. *J Appl Physiol* 110: 1549-1554, 2011.
9. Anderson JE and Wozniak AC. Satellite cell activation on fibers: modeling events in vivo--an invited review. *Can J Physiol Pharmacol* 82: 300-310, 2004.
10. Appell HJ, Soares JM and Duarte JA. Exercise, muscle damage and fatigue. *Sports Med* 13: 108-115, 1992.
11. Armstrong RB. Initial events in exercise-induced muscular injury. *Med Sci Sports Exerc* 22: 429-435, 1990.
12. Armstrong RB. Mechanisms of exercise-induced delayed onset muscular soreness: a brief review. *Med Sci Sports Exerc* 16: 529-538, 1984.
13. Armstrong RB, Ogilvie RW and Schwane JA. Eccentric exercise-induced injury to rat skeletal muscle. *J Appl Physiol* 54: 80-93, 1983.
14. Armstrong RB, Warren GL and Warren JA. Mechanisms of exercise-induced muscle fibre injury. *Sports Med* 12: 184-207, 1991.
15. Asmussen E. Observations on experimental muscular soreness. *Acta Rehum Scand* 2: 109-116, 1956.
16. Asmussen E. Positive and negative muscular work. *Acta Physiol Scand* 28: 364-382, 1953.
17. Baeza-Raja B and Munoz-Canoves P. p38 MAPK-induced nuclear factor-kappaB activity is required for skeletal muscle differentiation: role of interleukin-6. *Mol Biol Cell* 15: 2013-2026, 2004.
18. Baldwin AC, Stevenson SW and Dudley GA. Nonsteroidal anti-inflammatory therapy after eccentric exercise in healthy older individuals. *J Gerontol A Biol Sci Med Sci* 56: M510-M513, 2001.
19. Baldwin LA. Use of nonsteroidal anti-inflammatory drugs following exercise-induced muscle injury. *Sports Med* 33: 177-185, 2003.
20. Barnes MJ, Mundel T and Stannard SR. Acute alcohol consumption aggravates the decline in muscle performance following strenuous eccentric exercise. *J Sci Med Sport* 13: 189-193, 2009.

21. Bassett DR, Jr. Scientific contributions of A. V. Hill: exercise physiology pioneer. *J Appl Physiol* 93: 1567-1582, 2002.
22. Basu S, Binder RJ, Suto R, Anderson KM and Srivastava PK. Necrotic but not apoptotic cell death releases heat shock proteins, which deliver a partial maturation signal to dendritic cells and activate the NF-kappa B pathway. *Int Immunol* 12: 1539-1546, 2000.
23. Bautmans I, Njemini R, Lambert M, Demanet C and Mets T. Circulating acute phase mediators and skeletal muscle performance in hospitalized geriatric patients. *J Gerontol A Biol Sci Med Sci* 60: 361-367, 2005.
24. Beaton LJ, Allan DA, Tarnopolsky MA, Tiidus PM and Phillips SM. Contraction-induced muscle damage is unaffected by vitamin E supplementation. *Med Sci Sports Exerc* 34: 798-805, 2002.
25. Beaton LJ, Tarnopolsky MA and Phillips SM. Contraction-induced muscle damage in humans following calcium channel blocker administration. *J Physiol* 544: 849-859, 2002.
26. Beaton LJ, Tarnopolsky MA and Phillips SM. Variability in estimating eccentric contraction-induced muscle damage and inflammation in humans. *Can J Appl Physiol* 27: 516-526, 2002.
27. Behm DG, Baker KM, Kelland R and Lomond J. The effect of muscle damage on strength and fatigue deficits. *J Strength Cond Res* 15: 255-263, 2001.
28. Blaauw B, Canato M, Agatea L, Toniolo L, Mammucari C, Masiero E, Abraham R, Sandri M, Schiaffino S and Reggiani C. Inducible activation of Akt increases skeletal muscle mass and force without satellite cell activation. *FASEB J* 23: 3896-3905, 2009.
29. Black CD, Elder CP, Gorgey A and Dudley GA. High Specific Torque is Related to Lengthening Contraction Induced Skeletal Muscle Injury. *J Appl Physiol* 2007.
30. Boldrin L, Muntoni F and Morgan JE. Are human and mouse satellite cells really the same? *J Histochem Cytochem* 58: 941-955, 2010.
31. Bondesen BA, Mills ST, Kegley KM and Pavlath GK. The COX-2 pathway is essential during early stages of skeletal muscle regeneration. *Am J Physiol Cell Physiol* 287: C475-C483, 2004.
32. Bondesen BA, Mills ST and Pavlath GK. The COX-2 pathway regulates growth of atrophied muscle via multiple mechanisms. *Am J Physiol Cell Physiol* 290: C1651-C1659, 2006.
33. Bourgeois J, MacDougall D, MacDonald J and Tarnopolsky M. Naproxen does not alter indices of muscle damage in resistance-exercise trained men. *Med Sci Sports Exerc* 31: 4-9, 1999.
34. Boursinos LA, Karachalios T, Poultsides L and Malizos KN. Do steroids, conventional non-steroidal anti-inflammatory drugs and selective Cox-2 inhibitors adversely affect fracture healing? *J Musculoskelet Neuronal Interact* 9: 44-52, 2009.
35. Brenner IK, Natale VM, Vasilidou P, Moldoveanu AI, Shek PN and Shephard RJ. Impact of three different types of exercise on components of the inflammatory response. *Eur J Appl Physiol Occup Physiol* 80: 452-460, 1999.
36. Broholm C, Laye MJ, Brandt C, Vadalasetty R, Pilegaard H, Pedersen BK and Scheele C. LIF is a contraction-induced myokine stimulating human myocyte proliferation. *J Appl Physiol* 111: 251-259, 2011.

37. Brooks SV and Faulkner JA. Contraction-induced injury: recovery of skeletal muscles in young and old mice. *Am J Physiol* 258: C436-C442, 1990.
38. Brooks SV and Faulkner JA. Severity of contraction-induced injury is affected by velocity only during stretches of large strain. *J Appl Physiol* 91: 661-666, 2001.
39. Brooks SV, Zerba E and Faulkner JA. Injury to muscle fibres after single stretches of passive and maximally stimulated muscles in mice. *J Physiol* 488 (Pt 2): 459-469, 1995.
40. Brown S, Day S and Donnelly A. Indirect evidence of human skeletal muscle damage and collagen breakdown after eccentric muscle actions. *J Sports Sci* 17: 397-402, 1999.
41. Brown SJ, Child RB, Day SH and Donnelly AE. Exercise-induced skeletal muscle damage and adaptation following repeated bouts of eccentric muscle contractions. *J Sports Sci* 15: 215-222, 1997.
42. Brown SJ, Child RB, Donnelly AE, Saxton JM and Day SH. Changes in human skeletal muscle contractile function following stimulated eccentric exercise. *Eur J Appl Physiol Occup Physiol* 72: 515-521, 1996.
43. Bruunsgaard H, Galbo H, Halkjaer-Kristensen J, Johansen TL, MacLean DA and Pedersen BK. Exercise-induced increase in serum interleukin-6 in humans is related to muscle damage. *J Physiol* 499 (Pt 3): 833-841, 1997.
44. Bruunsgaard JC, Johansen IB, Egnér IM, Rana ZA and Gundersen K. Myonuclei acquired by overload exercise precede hypertrophy and are not lost on detraining. *Proc Natl Acad Sci U S A* 2010.
45. Buford TW, Cooke MB, Shelmadine BD, Hudson GM, Redd L and Willoughby DS. Effects of eccentric treadmill exercise on inflammatory gene expression in human skeletal muscle. *Appl Physiol Nutr Metab* 34: 745-753, 2009.
46. Buford TW, Cooke MB and Willoughby DS. Resistance exercise-induced changes of inflammatory gene expression within human skeletal muscle. *Eur J Appl Physiol* 2009.
47. Burd NA, Dickinson JM, LeMoine JK, Carroll CC, Sullivan BE, Haus JM, Jemiolo B, Trappe SW, Hughes GM, Sanders CE, Jr. and Trappe TA. Effect of a cyclooxygenase-2 inhibitor on postexercise muscle protein synthesis in humans. *Am J Physiol Endocrinol Metab* 2009.
48. Burd NA, Dickinson JM, LeMoine JK, Carroll CC, Sullivan BE, Haus JM, Jemiolo B, Trappe SW, Hughes GM, Sanders CE, Jr. and Trappe TA. Effect of a cyclooxygenase-2 inhibitor on postexercise muscle protein synthesis in humans. *Am J Physiol Endocrinol Metab* 298: E354-E361, 2010.
49. Byrne C, Twist C and Eston R. Neuromuscular function after exercise-induced muscle damage: theoretical and applied implications. *Sports Med* 34: 49-69, 2004.
50. Cavassani KA, Ishii M, Wen H, Schaller MA, Lincoln PM, Lukacs NW, Hogaboam CM and Kunkel SL. TLR3 is an endogenous sensor of tissue necrosis during acute inflammatory events. *J Exp Med* 205: 2609-2621, 2008.
51. Chapman D, Newton M, Sacco P and Nosaka K. Greater muscle damage induced by fast versus slow velocity eccentric exercise. *Int J Sports Med* 27: 591-598, 2006.
52. Chapman DW, Newton M, McGuigan M and Nosaka K. Effect of lengthening contraction velocity on muscle damage of the elbow flexors. *Med Sci Sports Exerc* 40: 926-933, 2008.

53. Chapman DW, Newton M, McGuigan MR and Nosaka K. Comparison between old and young men for responses to fast velocity maximal lengthening contractions of the elbow flexors. *Eur J Appl Physiol* 104: 531-539, 2008.
54. Chapman DW, Newton MJ, Zainuddin Z, Sacco P and Nosaka K. Work and peak torque during eccentric exercise do not predict changes in markers of muscle damage. *Br J Sports Med* 42: 585-591, 2008.
55. Charge SB and Rudnicki MA. Cellular and molecular regulation of muscle regeneration. *Physiol Rev* 84: 209-238, 2004.
56. Chazaud B, Brigitte M, Yacoub-Youssef H, Arnold L, Gherardi R, Sonnet C, Lafuste P and Chretien F. Dual and beneficial roles of macrophages during skeletal muscle regeneration. *Exerc Sport Sci Rev* 37: 18-22, 2009.
57. Chen CH, Nosaka K, Chen HL, Lin MJ, Tseng KW and Chen TC. Effects of Flexibility Training On Eccentric Exercise-Induced Muscle Damage. *Med Sci Sports Exerc* 2010.
58. Chen TC. Variability in muscle damage after eccentric exercise and the repeated bout effect. *Res Q Exerc Sport* 77: 362-371, 2006.
59. Chen YW, Hubal MJ, Hoffman EP, Thompson PD and Clarkson PM. Molecular responses of human muscle to eccentric exercise. *J Appl Physiol* 95: 2485-2494, 2003.
60. Child R, Brown S, Day S, Donnelly A, Roper H and Saxton J. Changes in indices of antioxidant status, lipid peroxidation and inflammation in human skeletal muscle after eccentric muscle actions. *Clin Sci (Lond)* 96: 105-115, 1999.
61. Childs A, Jacobs C, Kaminski T, Halliwell B and Leeuwenburgh C. Supplementation with vitamin C and N-acetyl-cysteine increases oxidative stress in humans after an acute muscle injury induced by eccentric exercise. *Free Radic Biol Med* 31: 745-753, 2001.
62. Clarkson PM, Hoffman EP, Zambraski E, Gordish-Dressman H, Kearns A, Hubal M, Harmon B and Devaney JM. ACTN3 and MLCK genotype associations with exertional muscle damage. *J Appl Physiol* 99: 564-569, 2005.
63. Clarkson PM and Hubal MJ. Are women less susceptible to exercise-induced muscle damage? *Curr Opin Clin Nutr Metab Care* 4: 527-531, 2001.
64. Clarkson PM and Hubal MJ. Exercise-induced muscle damage in humans. *Am J Phys Med Rehabil* 81: S52-S69, 2002.
65. Clarkson PM, Kearns AK, Rouzier P, Rubin R and Thompson PD. Serum creatine kinase levels and renal function measures in exertional muscle damage. *Med Sci Sports Exerc* 38: 623-627, 2006.
66. Clarkson PM and Newham DJ. Associations between muscle soreness, damage, and fatigue. *Adv Exp Med Biol* 384: 457-469, 1995.
67. Clarkson PM, Nosaka K and Braun B. Muscle function after exercise-induced muscle damage and rapid adaptation. *Med Sci Sports Exerc* 24: 512-520, 1992.
68. Close GL, Ashton T, McArdle A and MacLaren DP. The emerging role of free radicals in delayed onset muscle soreness and contraction-induced muscle injury. *Comp Biochem Physiol A Mol Integr Physiol* 142: 257-266, 2005.
69. Coffey VG, Zhong Z, Shield A, Canny BJ, Chibalin AV, Zierath JR and Hawley JA. Early signaling responses to divergent exercise stimuli in skeletal muscle from well-trained humans. *FASEB J* 20: 190-192, 2006.

70. Costill DL, Pascoe DD, Fink WJ, Robergs RA, Barr SI and Pearson D. Impaired muscle glycogen resynthesis after eccentric exercise. *J Appl Physiol* 69: 46-50, 1990.
71. Cramer RM, Aagaard P, Qvortrup K, Langberg H, Olesen J and Kjaer M. Myofibre damage in human skeletal muscle: effects of electrical stimulation versus voluntary contraction. *J Physiol* 583: 365-380, 2007.
72. Cramer RM, Langberg H, Magnusson P, Jensen CH, Schroder HD, Olesen JL, Suetta C, Teisner B and Kjaer M. Changes in satellite cells in human skeletal muscle after a single bout of high intensity exercise. *J Physiol* 558: 333-340, 2004.
73. Cramer RM, Langberg H, Teisner B, Magnusson P, Schroder HD, Olesen JL, Jensen CH, Koskinen S, Suetta C and Kjaer M. Enhanced procollagen processing in skeletal muscle after a single bout of eccentric loading in humans. *Matrix Biol* 23: 259-264, 2004.
74. Crenshaw AG, Friden J, Hargens AR, Lang GH and Thornell LE. Increased technetium uptake is not equivalent to muscle necrosis: scintigraphic, morphological and intramuscular pressure analyses of sore muscles after exercise. *Acta Physiol Scand* 148: 187-198, 1993.
75. Crenshaw AG, Karlsson S, Styf J, Backlund T and Friden J. Knee extension torque and intramuscular pressure of the vastus lateralis muscle during eccentric and concentric activities. *Eur J Appl Physiol Occup Physiol* 70: 13-19, 1995.
76. Crenshaw AG, Thornell LE and Friden J. Intramuscular pressure, torque and swelling for the exercise-induced sore vastus lateralis muscle. *Acta Physiol Scand* 152: 265-277, 1994.
77. Croisier JL, Camus G, Venneman I, Deby-Dupont G, Juchmes-Ferir A, Lamy M, Crielaard JM, Deby C and Duchateau J. Effects of training on exercise-induced muscle damage and interleukin 6 production. *Muscle Nerve* 22: 208-212, 1999.
78. Degterev A and Yuan J. Expansion and evolution of cell death programmes. *Nat Rev Mol Cell Biol* 9: 378-390, 2008.
79. Dehne N, Kerkweg U, Flohe SB, Brune B and Fandrey J. Activation of hypoxia-inducible factor 1 in skeletal muscle cells after exposure to damaged muscle cell debris. *Shock* 35: 632-638, 2011.
80. Deldicque L, Atherton P, Patel R, Theisen D, Nielens H, Rennie MJ and Francaux M. Effects of resistance exercise with and without creatine supplementation on gene expression and cell signaling in human skeletal muscle. *J Appl Physiol* 104: 371-378, 2008.
81. Dennis RA, Trappe TA, Simpson P, Carroll C, Huang BE, Nagarajan R, Bearden E, Gurley C, Duff GW, Evans WJ, Kornman K and Peterson CA. Interleukin-1 polymorphisms are associated with the inflammatory response in human muscle to acute resistance exercise. *J Physiol* 560: 617-626, 2004.
82. Devaney JM, Hoffman EP, Gordish-Dressman H, Kearns A, Zambraski E and Clarkson PM. IGF-II gene region polymorphisms related to exertional muscle damage. *J Appl Physiol* 102: 1815-1823, 2007.
83. Dey I, Lejeune M and Chadee K. Prostaglandin E2 receptor distribution and function in the gastrointestinal tract. *Br J Pharmacol* 149: 611-623, 2006.
84. Dreyer HC, Blanco CE, Sattler FR, Schroeder ET and Wiswell RA. Satellite cell numbers in young and older men 24 hours after eccentric exercise. *Muscle Nerve* 33: 242-253, 2006.

85. Duarte JA, Carvalho F, Bastos ML, Soares JM and Appell HJ. Do invading leucocytes contribute to the decrease in glutathione concentrations indicating oxidative stress in exercised muscle, or are they important for its recovery? *Eur J Appl Physiol Occup Physiol* 68: 48-53, 1994.
86. Evans WJ and Cannon JG. The metabolic effects of exercise-induced muscle damage. *Exerc Sport Sci Rev* 19: 99-125, 1991.
87. Falvo MJ and Bloomer RJ. Review of exercise-induced muscle injury: relevance for athletic populations. *Res Sports Med* 14: 65-82, 2006.
88. Faulkner JA, Brooks SV and Opiteck JA. Injury to skeletal muscle fibers during contractions: conditions of occurrence and prevention. *Phys Ther* 73: 911-921, 1993.
89. Faulkner JA and Carlson BM. Skeletal muscle regeneration: a historical perspective. *Fed Proc* 45: 1454-1455, 1986.
90. Feasson L, Stockholm D, Freyssenet D, Richard I, Duguez S, Beckmann JS and Denis C. Molecular adaptations of neuromuscular disease-associated proteins in response to eccentric exercise in human skeletal muscle. *J Physiol* 543: 297-306, 2002.
91. Feucht CL and Patel DR. Analgesics and anti-inflammatory medications in sports: use and abuse. *Pediatr Clin North Am* 57: 751-774, 2010.
92. Fielding RA, Manfredi TJ, Ding W, Fiatarone MA, Evans WJ and Cannon JG. Acute phase response in exercise. III. Neutrophil and IL-1 beta accumulation in skeletal muscle. *Am J Physiol* 265: R166-R172, 1993.
93. Foley JM, Jayaraman RC, Prior BM, Pivarnik JM and Meyer RA. MR measurements of muscle damage and adaptation after eccentric exercise. *J Appl Physiol* 87: 2311-2318, 1999.
94. Folkesson M, Mackey AL, Holm L, Kjaer M, Paulsen G, Raastad T, Henriksson J and Kadi F. Immunohistochemical changes in the expression of HSP27 in exercised human vastus lateralis muscle. *Acta Physiol (Oxf)* 194: 215-222, 2008.
95. Frangogiannis NG. The immune system and cardiac repair. *Pharmacol Res* 58: 88-111, 2008.
96. Friden J. Changes in human skeletal muscle induced by long-term eccentric exercise. *Cell Tissue Res* 236: 365-372, 1984.
97. Friden J, Kjorell U and Thornell LE. Delayed muscle soreness and cytoskeletal alterations: an immunocytological study in man. *Int J Sports Med* 5: 15-18, 1984.
98. Friden J and Lieber RL. Eccentric exercise-induced injuries to contractile and cytoskeletal muscle fibre components. *Acta Physiol Scand* 171: 321-326, 2001.
99. Friden J and Lieber RL. Segmental muscle fiber lesions after repetitive eccentric contractions. *Cell Tissue Res* 293: 165-171, 1998.
100. Friden J and Lieber RL. Serum creatine kinase level is a poor predictor of muscle function after injury. *Scand J Med Sci Sports* 11: 126-127, 2001.
101. Friden J, Sfakianos PN and Hargens AR. Muscle soreness and intramuscular fluid pressure: comparison between eccentric and concentric load. *J Appl Physiol* 61: 2175-2179, 1986.
102. Friden J, Sjostrom M and Ekblom B. A morphological study of delayed muscle soreness. *Experientia* 37: 506-507, 1981.
103. Friden J, Sjostrom M and Ekblom B. Myofibrillar damage following intense eccentric exercise in man. *Int J Sports Med* 4: 170-176, 1983.

104. Funk CD. Prostaglandins and leukotrienes: advances in eicosanoid biology. *Science* 294: 1871-1875, 2001.
105. Gibala MJ, Interisano SA, Tarnopolsky MA, Roy BD, MacDonald JR, Yarasheski KE and MacDougall JD. Myofibrillar disruption following acute concentric and eccentric resistance exercise in strength-trained men. *Can J Physiol Pharmacol* 78: 656-661, 2000.
106. Gibala MJ, MacDougall JD, Tarnopolsky MA, Stauber WT and Elorriaga A. Changes in human skeletal muscle ultrastructure and force production after acute resistance exercise. *J Appl Physiol* 78: 702-708, 1995.
107. Gissel H and Clausen T. Excitation-induced Ca²⁺ influx and skeletal muscle cell damage. *Acta Physiol Scand* 171: 327-334, 2001.
108. Gordon AM, Huxley AF and Julian FJ. Tension development in highly stretched vertebrate muscle fibres. *J Physiol* 184: 143-169, 1966.
109. Gordon AM, Huxley AF and Julian FJ. The variation in isometric tension with sarcomere length in vertebrate muscle fibres. *J Physiol* 184: 170-192, 1966.
110. Gorski T, Cadore EL, Pinto SS, da Silva EM, Correa CS, Beltrami FG and Kruel LF. Use of NSAIDs in triathletes: prevalence, level of awareness and reasons for use. *Br J Sports Med* 45: 85-90, 2011.
111. Granado M, Martin AI, Villanua MA and Lopez-Calderon A. Experimental arthritis inhibits the insulin-like growth factor-I axis and induces muscle wasting through cyclooxygenase-2 activation. *Am J Physiol Endocrinol Metab* 292: E1656-E1665, 2007.
112. Gregory JE, Morgan DL, Allen TJ and Proske U. The shift in muscle's length-tension relation after exercise attributed to increased series compliance. *Eur J Appl Physiol* 99: 431-441, 2007.
113. Gulbin JP and Gaffney PT. Identical twins are discordant for markers of eccentric exercise-induced muscle damage. *Int J Sports Med* 23: 471-476, 2002.
114. Gundersen K and Bruusgaard JC. Nuclear domains during muscle atrophy: nuclei lost or paradigm lost? *J Physiol* 586: 2675-2681, 2008.
115. Halkjaer-Kristensen J and Ingemann-Hansen T. Variations in single fibre areas and fibre composition in needle biopsies from the human quadriceps muscle. *Scand J Clin Lab Invest* 41: 391-395, 1981.
116. Hamada K, Vannier E, Sacheck JM, Witsell AL and Roubenoff R. Senescence of human skeletal muscle impairs the local inflammatory cytokine response to acute eccentric exercise. *FASEB J* 19: 264-266, 2005.
117. Harris TB, Ferrucci L, Tracy RP, Corti MC, Wacholder S, Ettinger WH, Jr., Heimovitz H, Cohen HJ and Wallace R. Associations of elevated interleukin-6 and C-reactive protein levels with mortality in the elderly. *Am J Med* 106: 506-512, 1999.
118. Hawke TJ and Garry DJ. Myogenic satellite cells: physiology to molecular biology. *J Appl Physiol* 91: 534-551, 2001.
119. Hellsten Y, Frandsen U, Orthenblad N, Sjodin B and Richter EA. Xanthine oxidase in human skeletal muscle following eccentric exercise: a role in inflammation. *J Physiol* 498 (Pt 1): 239-248, 1997.
120. Hersh EV, Lally ET and Moore PA. Update on cyclooxygenase inhibitors: has a third COX isoform entered the fray? *Curr Med Res Opin* 21: 1217-1226, 2005.

121. Hikida RS, Staron RS, Hagerman FC, Sherman WM and Costill DL. Muscle fiber necrosis associated with human marathon runners. *J Neurol Sci* 59: 185-203, 1983.
122. Hill AV. The heat of shortening and the dynamic constants of muscle. *Proc R Soc Lond B Biol Sci* 126: 136-195, 1938.
123. Hill AV. The mechanics of voluntary muscle. *Lancet* 261: 947-951, 1951.
124. Hirose L, Nosaka K, Newton M, Laveder A, Kano M, Peake J and Suzuki K. Changes in inflammatory mediators following eccentric exercise of the elbow flexors. *Exerc Immunol Rev* 10: 75-90, 2004.
125. Hitt A, Graves E and McCarthy DO. Indomethacin preserves muscle mass and reduces levels of E3 ligases and TNF receptor type 1 in the gastrocnemius muscle of tumor-bearing mice. *Res Nurs Health* 28: 56-66, 2005.
126. Hortobagyi T, Houmard J, Fraser D, Dudek R, Lambert J and Tracy J. Normal forces and myofibrillar disruption after repeated eccentric exercise. *J Appl Physiol* 84: 492-498, 1998.
127. Hough T. Ergographic studies in muscular soreness. *Am J Physiol* 7: 76-92, 1902.
128. Howell JN, Chleboun G and Conatser R. Muscle stiffness, strength loss, swelling and soreness following exercise-induced injury in humans. *J Physiol* 464: 183-196, 1993.
129. Hubal MJ, Chen TC, Thompson PD and Clarkson PM. Inflammatory gene changes associated with the repeated-bout effect. *Am J Physiol Regul Integr Comp Physiol* 294: R1628-R1637, 2008.
130. Hubal MJ, Devaney JM, Hoffman EP, Zambraski EJ, Gordish-Dressman H, Kearns AK, Larkin JS, Adham K, Patel RR and Clarkson PM. CCL2 and CCR2 polymorphisms are associated with markers of exercise-induced skeletal muscle damage. *J Appl Physiol* 108: 1651-1658, 2010.
131. Hubal MJ, Rubinstein SR and Clarkson PM. Mechanisms of variability in strength loss after muscle-lengthening actions. *Med Sci Sports Exerc* 39: 461-468, 2007.
132. Huxley AF. The activation of striated muscle and its mechanical response. *Proc R Soc Lond B Biol Sci* 178: 1-27, 1971.
133. Huxley HE. Memories of early work on muscle contraction and regulation in the 1950's and 1960's. *Biochem Biophys Res Commun* 369: 34-42, 2008.
134. Jackson MJ, Jones DA and Edwards RH. Experimental skeletal muscle damage: the nature of the calcium-activated degenerative processes. *Eur J Clin Invest* 14: 369-374, 1984.
135. Jackson RC. Exercise-induced renal failure and muscle damage. *Proc R Soc Med* 63: 566-570, 1970.
136. Jarvinen TA, Jarvinen TL, Kaariainen M, Kalimo H and Jarvinen M. Muscle injuries: biology and treatment. *Am J Sports Med* 33: 745-764, 2005.
137. Jones DA, Newham DJ, Round JM and Tolfree SE. Experimental human muscle damage: morphological changes in relation to other indices of damage. *J Physiol* 375: 435-448, 1986.
138. Jones DA, Newham DJ and Torgan C. Mechanical influences on long-lasting human muscle fatigue and delayed-onset pain. *J Physiol* 412: 415-427, 1989.
139. Jozsi AC, Dupont-Versteegden EE, Taylor-Jones JM, Evans WJ, Trappe TA, Campbell WW and Peterson CA. Aged human muscle demonstrates an altered gene expression profile consistent with an impaired response to exercise. *Mech Ageing Dev* 120: 45-56, 2000.

140. Julian FJ and Morgan DL. Intersarcomere dynamics during fixed-end tetanic contractions of frog muscle fibres. *J Physiol* 293: 365-378, 1979.
141. Julian FJ and Morgan DL. The effect on tension of non-uniform distribution of length changes applied to frog muscle fibres. *J Physiol* 293: 379-392, 1979.
142. Karamouzis M, Langberg H, Skovgaard D, Bulow J, Kjaer M and Saltin B. In situ microdialysis of intramuscular prostaglandin and thromboxane in contracting skeletal muscle in humans. *Acta Physiol Scand* 171: 71-76, 2001.
143. Kasperek GJ and Snider RD. The susceptibility to exercise-induced muscle damage increases as rats grow larger. *Experientia* 41: 616-617, 1985.
144. Katz B. The relation between force and speed in muscular contraction. *J Physiol* 96: 45-64, 1939.
145. Kingsley MI, Kilduff LP, McEneny J, Dietzig RE and Benton D. Phosphatidylserine supplementation and recovery following downhill running. *Med Sci Sports Exerc* 38: 1617-1625, 2006.
146. Knochel JP. Rhabdomyolysis and myoglobinuria. *Annu Rev Med* 33: 435-443, 1982.
147. Koh TJ, Peterson JM, Pizza FX and Brooks SV. Passive stretches protect skeletal muscle of adult and old mice from lengthening contraction-induced injury. *J Gerontol A Biol Sci Med Sci* 58: 592-597, 2003.
148. Krentz JR and Farthing JP. Neural and morphological changes in response to a 20-day intense eccentric training protocol. *Eur J Appl Physiol* 110: 333-340, 2010.
149. Krentz JR, Quest B, Farthing JP, Quest DW and Chilibeck PD. The effects of ibuprofen on muscle hypertrophy, strength, and soreness during resistance training. *Appl Physiol Nutr Metab* 33: 470-475, 2008.
150. Kuipers H, Keizer HA, Verstappen FT and Costill DL. Influence of a prostaglandin-inhibiting drug on muscle soreness after eccentric work. *Int J Sports Med* 6: 336-339, 1985.
151. Langberg H, Olesen JL, Gemmer C and Kjaer M. Substantial elevation of interleukin-6 concentration in peritendinous tissue, in contrast to muscle, following prolonged exercise in humans. *J Physiol* 542: 985-990, 2002.
152. Lapointe BM, Fremont P and Cote CH. Adaptation to lengthening contractions is independent of voluntary muscle recruitment but relies on inflammation. *Am J Physiol Regul Integr Comp Physiol* 282: R323-R329, 2002.
153. Lapointe BM, Frenette J and Cote CH. Lengthening contraction-induced inflammation is linked to secondary damage but devoid of neutrophil invasion. *J Appl Physiol* 92: 1995-2004, 2002.
154. Lauritzen F, Paulsen G, Raastad T, Bergersen LH and Owe SG. Gross ultrastructural changes and necrotic fiber segments in elbow flexor muscles after maximal voluntary eccentric action in humans. *J Appl Physiol* 2009.
155. Lavender AP and 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* 97: 619-626, 2006.
156. Lexell J and Taylor CC. Variability in muscle fibre areas in whole human quadriceps muscle. How much and why? *Acta Physiol Scand* 136: 561-568, 1989.
157. Lieber RL and Friden J. Mechanisms of muscle injury after eccentric contraction. *J Sci Med Sport* 2: 253-265, 1999.

158. Lieber RL and Friden J. Mechanisms of muscle injury gleaned from animal models. *Am J Phys Med Rehabil* 81: S70-S79, 2002.
159. Lieber RL and Friden J. Morphologic and mechanical basis of delayed-onset muscle soreness. *J Am Acad Orthop Surg* 10: 67-73, 2002.
160. Lieber RL and Friden J. Muscle damage is not a function of muscle force but active muscle strain. *J Appl Physiol* 74: 520-526, 1993.
161. Lieber RL, Thornell LE and Friden J. Muscle cytoskeletal disruption occurs within the first 15 min of cyclic eccentric contraction. *J Appl Physiol* 80: 278-284, 1996.
162. Lieber RL, Woodburn TM and Friden J. Muscle damage induced by eccentric contractions of 25% strain. *J Appl Physiol* 70: 2498-2507, 1991.
163. Lindstrom M and Thornell LE. New multiple labelling method for improved satellite cell identification in human muscle: application to a cohort of power-lifters and sedentary men. *Histochem Cell Biol* 132: 141-157, 2009.
164. Lockhart NC and Brooks SV. Neutrophil accumulation following passive stretches contributes to adaptations that reduce contraction-induced skeletal muscle injury in mice. *J Appl Physiol* 104: 1109-1115, 2008.
165. Louis E, Raue U, Yang Y, Jemiolo B and Trappe S. Time course of proteolytic, cytokine, and myostatin gene expression after acute exercise in human skeletal muscle. *J Appl Physiol* 103: 1744-1751, 2007.
166. Lovering RM and De Deyne PG. Contractile function, sarcolemma integrity, and the loss of dystrophin after skeletal muscle eccentric contraction-induced injury. *Am J Physiol Cell Physiol* 286: C230-C238, 2004.
167. Lynch GS and Faulkner JA. Contraction-induced injury to single muscle fibers: velocity of stretch does not influence the force deficit. *Am J Physiol* 275: C1548-C1554, 1998.
168. MacIntyre DL, Reid WD, Lyster DM and McKenzie DC. Different effects of strenuous eccentric exercise on the accumulation of neutrophils in muscle in women and men. *Eur J Appl Physiol* 81: 47-53, 2000.
169. MacIntyre DL, Reid WD, Lyster DM, Szasz IJ and McKenzie DC. Presence of WBC, decreased strength, and delayed soreness in muscle after eccentric exercise. *J Appl Physiol* 80: 1006-1013, 1996.
170. MacIntyre DL, Reid WD and McKenzie DC. Delayed muscle soreness. The inflammatory response to muscle injury and its clinical implications. *Sports Med* 20: 24-40, 1995.
171. Mackey AL, Bojsen-Moller J, Qvortrup K, Langberg H, Suetta C, Kalliokoski KK, Kjaer M and Magnusson SP. Evidence of skeletal muscle damage following electrically stimulated isometric muscle contractions in humans. *J Appl Physiol* 105: 1620-1627, 2008.
172. Mackey AL, Brandstetter S, Schjerling P, Bojsen-Moller J, Qvortrup K, Pedersen MM, Doessing S, Kjaer M, Magnusson SP and Langberg H. Sequenced response of extracellular matrix adhesion and fibrotic regulators after muscle damage is involved in protection against future injury in human skeletal muscle. *FASEB J* 25: 1943-1959, 2011.
173. Mackey AL, Donnelly AE, Turpeenniemi-Hujanen T and Roper HP. Skeletal muscle collagen content in humans after high-force eccentric contractions. *J Appl Physiol* 97: 197-203, 2004.

174. Mackey AL, Kjaer M, Dandanell S, Mikkelsen KH, Holm L, Dossing S, Kadi F, Koskinen SO, Jensen CH, Schroder HD and Langberg H. The influence of anti-inflammatory medication on exercise-induced myogenic precursor cell responses in humans. *J Appl Physiol* 103: 425-431, 2007.
175. MacNeil LG, Baker SK, Stevic I and Tarnopolsky MA. 17beta-estradiol attenuates exercise-induced neutrophil infiltration in men. *Am J Physiol Regul Integr Comp Physiol* 300: R1443-R1451, 2011.
176. Macpherson PC, Schork MA and Faulkner JA. Contraction-induced injury to single fiber segments from fast and slow muscles of rats by single stretches. *Am J Physiol* 271: C1438-C1446, 1996.
177. Mahoney DJ, Safdar A, Parise G, Melov S, Fu M, Macneil L, Kaczor JJ, Payne ET and Tarnopolsky MA. Gene expression profiling in human skeletal muscle during recovery from eccentric exercise. *Am J Physiol Regul Integr Comp Physiol* 2008.
178. Malm C. Exercise immunology: a skeletal muscle perspective. *Exerc Immunol Rev* 8: 116-167, 2002.
179. Malm C. Exercise-induced muscle damage and inflammation: fact or fiction? *Acta Physiol Scand* 171: 233-239, 2001.
180. Malm C, Nyberg P, Engstrom M, Sjodin B, Lenkei R, Ekblom B and Lundberg I. Immunological changes in human skeletal muscle and blood after eccentric exercise and multiple biopsies. *J Physiol* 529 Pt 1: 243-262, 2000.
181. Malm C, Sjodin TL, Sjoberg B, Lenkei R, Renstrom P, Lundberg IE and Ekblom B. Leukocytes, cytokines, growth factors and hormones in human skeletal muscle and blood after uphill or downhill running. *J Physiol* 556: 983-1000, 2004.
182. Manfredi TG, Fielding RA, O'Reilly KP, Meredith CN, Lee HY and Evans WJ. Plasma creatine kinase activity and exercise-induced muscle damage in older men. *Med Sci Sports Exerc* 23: 1028-1034, 1991.
183. Marginson V, Rowlands AV, Gleeson NP and Eston RG. Comparison of the symptoms of exercise-induced muscle damage after an initial and repeated bout of plyometric exercise in men and boys. *J Appl Physiol* 99: 1174-1181, 2005.
184. Mathes AL and Lafyatis R. Role for Toll-like receptor 3 in muscle regeneration after cardiotoxin injury. *Muscle Nerve* 43: 733-740, 2011.
185. Mauro A. Satellite cell of skeletal muscle fibers. *J Biophys Biochem Cytol* 9: 493-495, 1961.
186. McArdle A and Jackson MJ. Exercise, oxidative stress and ageing. *J Anat* 197 Pt 4: 539-541, 2000.
187. McArdle A, Pattwell D, Vasilaki A, Griffiths RD and Jackson MJ. Contractile activity-induced oxidative stress: cellular origin and adaptive responses. *Am J Physiol Cell Physiol* 280: C621-C627, 2001.
188. McArdle A, van der Meulen JH, Catapano M, Symons MC, Faulkner JA and Jackson MJ. Free radical activity following contraction-induced injury to the extensor digitorum longus muscles of rats. *Free Radic Biol Med* 26: 1085-1091, 1999.
189. McCarthy DO, Whitney P, Hitt A and Al-Majid S. Indomethacin and ibuprofen preserve gastrocnemius muscle mass in mice bearing the colon-26 adenocarcinoma. *Res Nurs Health* 27: 174-184, 2004.
190. McCarthy JJ and Esser KA. Counterpoint: Satellite cell addition is not obligatory for skeletal muscle hypertrophy. *J Appl Physiol* 103: 1100-1102, 2007.

191. McCarthy JJ, Mula J, Miyazaki M, Erfani R, Garrison K, Farooqui AB, Srikuea R, Lawson BA, Grimes B, Keller C, Van ZG, Campbell KS, Esser KA, Dupont-Versteegden EE and Peterson CA. Effective fiber hypertrophy in satellite cell-depleted skeletal muscle. *Development* 138: 3657-3666, 2011.
192. McCully KK and Faulkner JA. Characteristics of lengthening contractions associated with injury to skeletal muscle fibers. *J Appl Physiol* 61: 293-299, 1986.
193. McCully KK and Faulkner JA. Injury to skeletal muscle fibers of mice following lengthening contractions. *J Appl Physiol* 59: 119-126, 1985.
194. McHugh MP. Recent advances in the understanding of the repeated bout effect: the protective effect against muscle damage from a single bout of eccentric exercise. *Scand J Med Sci Sports* 13: 88-97, 2003.
195. McHugh MP, Connolly DA, Eston RG, Kremenec IJ, Nicholas SJ and Gleim GW. The role of passive muscle stiffness in symptoms of exercise-induced muscle damage. *Am J Sports Med* 27: 594-599, 1999.
196. McKay BR, De LM, Johnston AP, O'Reilly CE, Phillips SM, Tarnopolsky MA and Parise G. Association of interleukin-6 signalling with the muscle stem cell response following muscle-lengthening contractions in humans. *PLoS One* 4: e6027, 2009.
197. McKay BR, Toth KG, Tarnopolsky MA and Parise G. Satellite cell number and cell cycle kinetics in response to acute myotrauma in humans: immunohistochemistry versus flow cytometry. *J Physiol* 588: 3307-3320, 2010.
198. Mehallo CJ, Drezner JA and Bytowski JR. Practical management: nonsteroidal antiinflammatory drug (NSAID) use in athletic injuries. *Clin J Sport Med* 16: 170-174, 2006.
199. Mendias CL, Tatsumi R and Allen RE. Role of cyclooxygenase-1 and -2 in satellite cell proliferation, differentiation, and fusion. *Muscle Nerve* 30: 497-500, 2004.
200. Michna H. Ultrastructural features of skeletal muscle in mice after physical exercise: its relation to the pathogenesis of leucocyte invasion. *Acta Anat (Basel)* 134: 276-282, 1989.
201. Mikkelsen UR, Helmark IC, Kjaer M and Langberg H. Prostaglandin synthesis can be inhibited locally by infusion of NSAIDs through microdialysis catheters in human skeletal muscle. *J Appl Physiol* 2007.
202. Mikkelsen UR, Langberg H, Helmark IC, Skovgaard D, Andersen LL, Kjaer M and Mackey AL. Local NSAID infusion inhibits satellite cell proliferation in human skeletal muscle after eccentric exercise. *J Appl Physiol* 107: 1600-1611, 2009.
203. Mikkelsen UR, Schjerling P, Helmark IC, Reitelseder S, Holm L, Skovgaard D, Langberg H, Kjaer M and Heinemeier KM. Local NSAID infusion does not affect protein synthesis and gene expression in human muscle after eccentric exercise. *Scand J Med Sci Sports* 21: 630-644, 2011.
204. Mishra DK, Friden J, Schmitz MC and Lieber RL. Anti-inflammatory medication after muscle injury. A treatment resulting in short-term improvement but subsequent loss of muscle function. *J Bone Joint Surg Am* 77: 1510-1519, 1995.
205. Morgan DL. New insights into the behavior of muscle during active lengthening. *Biophys J* 57: 209-221, 1990.
206. Morgan DL and Allen DG. Early events in stretch-induced muscle damage. *J Appl Physiol* 87: 2007-2015, 1999.
207. Morgan DL and Proske U. Popping sarcomere hypothesis explains stretch-induced muscle damage. *Clin Exp Pharmacol Physiol* 31: 541-545, 2004.

208. Morozov VI, Usenko TN and Rogozkin VA. Neutrophil antiserum response to decrease in proteolytic activity in loaded rat muscle. *Eur J Appl Physiol* 84: 195-200, 2001.
209. Murphy RM, Goodman CA, McKenna MJ, Bennie J, Leikis M and Lamb GD. Calpain-3 is autolyzed and hence activated in human skeletal muscle 24 h following a single bout of eccentric exercise. *J Appl Physiol* 103: 926-931, 2007.
210. Newham DJ. The consequences of eccentric contractions and their relationship to delayed onset muscle pain. *Eur J Appl Physiol Occup Physiol* 57: 353-359, 1988.
211. Newham DJ, Jones DA and Edwards RH. Large delayed plasma creatine kinase changes after stepping exercise. *Muscle Nerve* 6: 380-385, 1983.
212. Newham DJ, Jones DA, Ghosh G and Aurora P. Muscle fatigue and pain after eccentric contractions at long and short length. *Clin Sci (Lond)* 74: 553-557, 1988.
213. Newham DJ, McPhail G, Mills KR and Edwards RH. Ultrastructural changes after concentric and eccentric contractions of human muscle. *J Neurol Sci* 61: 109-122, 1983.
214. Nielsen AR, Mounier R, Plomgaard P, Mortensen OH, Penkowa M, Speersneider T, Pilegaard H and Pedersen BK. Expression of interleukin-15 in human skeletal muscle effect of exercise and muscle fibre type composition. *J Physiol* 584: 305-312, 2007.
215. Nieman DC, Davis JM, Brown VA, Henson DA, Dumke CL, Utter AC, Vinci DM, Downs MF, Smith JC, Carson J, Brown A, McAnulty SR and McAnulty LS. Influence of carbohydrate ingestion on immune changes after 2 h of intensive resistance training. *J Appl Physiol* 96: 1292-1298, 2004.
216. Nieman DC, Dumke CL, Henson DA, McAnulty SR, Gross SJ and Lind RH. Muscle damage is linked to cytokine changes following a 160-km race. *Brain Behav Immun* 19: 398-403, 2005.
217. Nosaka K, Chapman D, Newton M and Sacco P. Is isometric strength loss immediately after eccentric exercise related to changes in indirect markers of muscle damage? *J Appl Physiol Nutr Metab* 31: 313-319, 2006.
218. Nosaka K and Clarkson PM. Variability in serum creatine kinase response after eccentric exercise of the elbow flexors. *Int J Sports Med* 17: 120-127, 1996.
219. Nosaka K, Newton M and Sacco P. Delayed-onset muscle soreness does not reflect the magnitude of eccentric exercise-induced muscle damage. *Scand J Med Sci Sports* 12: 337-346, 2002.
220. Nosaka K, Sakamoto K, Newton M and Sacco P. How long does the protective effect on eccentric exercise-induced muscle damage last? *Med Sci Sports Exerc* 33: 1490-1495, 2001.
221. Nosaka K, Sakamoto K, Newton M and Sacco P. The repeated bout effect of reduced-load eccentric exercise on elbow flexor muscle damage. *Eur J Appl Physiol* 85: 34-40, 2001.
222. Novak ML, Billich W, Smith SM, Sukhija KB, McLoughlin TJ, Hornberger TA and Koh TJ. COX-2 inhibitor reduces skeletal muscle hypertrophy in mice. *Am J Physiol Regul Integr Comp Physiol* 296: R1132-R1139, 2009.
223. Nurenberg P, Giddings CJ, Stray-Gundersen J, Fleckenstein JL, Gonyea WJ and Peshock RM. MR imaging-guided muscle biopsy for correlation of increased signal intensity with ultrastructural change and delayed-onset muscle soreness after exercise. *Radiology* 184: 865-869, 1992.

224. O'Grady M, Hackney AC, Schneider K, Bossen E, Steinberg K, Douglas JM, Jr., Murray WJ and Watkins WD. Diclofenac sodium (Voltaren) reduced exercise-induced injury in human skeletal muscle. *Med Sci Sports Exerc* 32: 1191-1196, 2000.
225. O'Reilly C, McKay B, Phillips S, Tarnopolsky M and Parise G. Hepatocyte growth factor (HGF) and the satellite cell response following muscle lengthening contractions in humans. *Muscle Nerve* 38: 1434-1442, 2008.
226. O'Reilly KP, Warhol MJ, Fielding RA, Frontera WR, Meredith CN and Evans WJ. Eccentric exercise-induced muscle damage impairs muscle glycogen repletion. *J Appl Physiol* 63: 252-256, 1987.
227. Paddon-Jones D, Keech A, Lonergan A and Abernethy P. Differential expression of muscle damage in humans following acute fast and slow velocity eccentric exercise. *J Sci Med Sport* 8: 255-263, 2005.
228. Paulsen G, Benestad HB, Strom-Gundersen I, Morkrid L, Lappegard KT and Raastad T. Delayed leukocytosis and cytokine response to high-force eccentric exercise. *Med Sci Sports Exerc* 37: 1877-1883, 2005.
229. Paulsen G, Cramer R, Benestad HB, Fjeld JG, Morkrid L, Hallen J and Raastad T. Time course of leukocyte accumulation in human muscle after eccentric exercise. *Med Sci Sports Exerc* 42: 75-85, 2010.
230. Paulsen G, Egner IM, Drange M, Langberg H, Benestad HB, Fjeld JG, Hallen J and Raastad T. A COX-2 inhibitor reduces muscle soreness, but does not influence recovery and adaptation after eccentric exercise. *Scand J Med Sci Sports* 20: e195-e207, 2010.
231. Peake J, Della GP and Cameron-Smith D. Aging and its effects on inflammation in skeletal muscle at rest and following exercise-induced muscle injury. *Am J Physiol Regul Integr Comp Physiol* 298: R1485-R1495, 2010.
232. Peake J, Nosaka K and Suzuki K. Characterization of inflammatory responses to eccentric exercise in humans. *Exerc Immunol Rev* 11: 64-85, 2005.
233. Peake J, Wilson G, Hordern M, Suzuki K, Yamaya K, Nosaka K, Mackinnon L and Coombes JS. Changes in neutrophil surface receptor expression, degranulation, and respiratory burst activity after moderate- and high-intensity exercise. *J Appl Physiol* 97: 612-618, 2004.
234. Peake JM, Nosaka K, Muthalib M and Suzuki K. Systemic inflammatory responses to maximal versus submaximal lengthening contractions of the elbow flexors. *Exerc Immunol Rev* 12: 72-85, 2006.
235. Peake JM, Suzuki K, Hordern M, Wilson G, Nosaka K and Coombes JS. Plasma cytokine changes in relation to exercise intensity and muscle damage. *Eur J Appl Physiol* 95: 514-521, 2005.
236. Peake JM, Suzuki K, Wilson G, Hordern M, Nosaka K, Mackinnon L and Coombes JS. Exercise-induced muscle damage, plasma cytokines, and markers of neutrophil activation. *Med Sci Sports Exerc* 37: 737-745, 2005.
237. Pedersen BK. Edward F. Adolph distinguished lecture: muscle as an endocrine organ: IL-6 and other myokines. *J Appl Physiol* 107: 1006-1014, 2009.
238. Pedersen BK. Muscles and their myokines. *J Exp Biol* 214: 337-346, 2011.
239. Petersen EW, Ostrowski K, Ibfelt T, Richelle M, Offord E, Halkjaer-Kristensen J and Pedersen BK. Effect of vitamin supplementation on cytokine response and on muscle damage after strenuous exercise. *Am J Physiol Cell Physiol* 280: C1570-C1575, 2001.

240. Peterson JM, Feeback KD, Baas JH and Pizza FX. Tumor necrosis factor- α promotes the accumulation of neutrophils and macrophages in skeletal muscle. *J Appl Physiol* 101: 1394-1399, 2006.
241. Peterson JM, Trappe TA, Mylona E, White F, Lambert CP, Evans WJ and Pizza FX. Ibuprofen and acetaminophen: effect on muscle inflammation after eccentric exercise. *Med Sci Sports Exerc* 35: 892-896, 2003.
242. Phillips T, Childs AC, Dreon DM, Phinney S and Leeuwenburgh C. A dietary supplement attenuates IL-6 and CRP after eccentric exercise in untrained males. *Med Sci Sports Exerc* 35: 2032-2037, 2003.
243. Pizza FX, Koh TJ, McGregor SJ and Brooks SV. Muscle inflammatory cells after passive stretches, isometric contractions, and lengthening contractions. *J Appl Physiol* 92: 1873-1878, 2002.
244. Prasartwuth O, Taylor JL and Gandevia SC. Maximal force, voluntary activation and muscle soreness after eccentric damage to human elbow flexor muscles. *J Physiol* 567: 337-348, 2005.
245. Proske U and Morgan DL. Muscle damage from eccentric exercise: mechanism, mechanical signs, adaptation and clinical applications. *J Physiol* 537: 333-345, 2001.
246. Przybyla B, Gurley C, Harvey JF, Bearden E, Kortebein P, Evans WJ, Sullivan DH, Peterson CA and Dennis RA. Aging alters macrophage properties in human skeletal muscle both at rest and in response to acute resistance exercise. *Exp Gerontol* 41: 320-327, 2006.
247. Pyne DB. Exercise-induced muscle damage and inflammation: a review. *Aust J Sci Med Sport* 26: 49-58, 1994.
248. Raastad T, Glomsheller T, Bjoro T and Hallen J. Recovery of skeletal muscle contractility and hormonal responses to strength exercise after two weeks of high-volume strength training. *Scand J Med Sci Sports* 13: 159-168, 2003.
249. Raastad T and Hallen J. Recovery of skeletal muscle contractility after high- and moderate-intensity strength exercise. *Eur J Appl Physiol* 82: 206-214, 2000.
250. Raastad T, Owe SG, Paulsen G, Enns D, Overgaard K, Crameri R, Kiil S, Belcastro A, Bergersen L and Hallen J. Changes in calpain activity, muscle structure, and function after eccentric exercise. *Med Sci Sports Exerc* 42: 86-95, 2010.
251. Raastad T, Risoy BA, Benestad HB, Fjeld JG and Hallen J. Temporal relation between leukocyte accumulation in muscles and halted recovery 10-20 h after strength exercise. *J Appl Physiol* 95: 2503-2509, 2003.
252. Raj DA, Booker TS and Belcastro AN. Striated muscle calcium-stimulated cysteine protease (calpain-like) activity promotes myeloperoxidase activity with exercise. *Pflugers Arch* 435: 804-809, 1998.
253. Raue U, Slivka D, Jemiolo B, Hollon C and Trappe S. Proteolytic gene expression differs at rest and after resistance exercise between young and old women. *J Gerontol A Biol Sci Med Sci* 62: 1407-1412, 2007.
254. Rieu I, Magne H, Savary-Auzeloux I, Averous J, Bos C, Peyron MA, Combaret L and Dardevet D. Reduction of low grade inflammation restores blunting of postprandial muscle anabolism and limits sarcopenia in old rats. *J Physiol* 587: 5483-5492, 2009.

255. Rodenburg JB, Bar PR and De Boer RW. Relations between muscle soreness and biochemical and functional outcomes of eccentric exercise. *J Appl Physiol* 74: 2976-2983, 1993.
256. Ross ML, Halson SL, Suzuki K, Garnham A, Hawley JA, Cameron-Smith D and Peake JM. Cytokine responses to carbohydrate ingestion during recovery from exercise-induced muscle injury. *J Interferon Cytokine Res* 30: 329-337, 2010.
257. Round JM, Jones DA and Cambridge G. Cellular infiltrates in human skeletal muscle: exercise induced damage as a model for inflammatory muscle disease? *J Neurol Sci* 82: 1-11, 1987.
258. Salminen A, Hongisto K and Vihko V. Lysosomal changes related to exercise injuries and training-induced protection in mouse skeletal muscle. *Acta Physiol Scand* 120: 15-19, 1984.
259. Salminen A and Vihko V. Autophagic response to strenuous exercise in mouse skeletal muscle fibers. *Virchows Arch B Cell Pathol Incl Mol Pathol* 45: 97-106, 1984.
260. Salminen A and Vihko V. Exercise myopathy: selectively enhanced proteolytic capacity in rat skeletal muscle after prolonged running. *Exp Mol Pathol* 38: 61-68, 1983.
261. Sambasivan R, Yao R, Kissenpfennig A, Van WL, Paldi A, Gayraud-Morel B, Gue-nou H, Malissen B, Tajbakhsh S and Galy A. Pax7-expressing satellite cells are indispensable for adult skeletal muscle regeneration. *Development* 138: 3647-3656, 2011.
262. Sayers SP and Clarkson PM. Exercise-induced rhabdomyolysis. *Curr Sports Med Rep* 1: 59-60, 2002.
263. Sayers SP and Clarkson PM. Force recovery after eccentric exercise in males and females. *Eur J Appl Physiol* 84: 122-126, 2001.
264. Sayers SP, Clarkson PM, Rouzier PA and Kamen G. Adverse events associated with eccentric exercise protocols: six case studies. *Med Sci Sports Exerc* 31: 1697-1702, 1999.
265. Sayers SP, Knight CA and Clarkson PM. Neuromuscular variables affecting the magnitude of force loss after eccentric exercise. *J Sports Sci* 21: 403-410, 2003.
266. Schubert W, Zimmermann K, Cramer M and Starzinski-Powitz A. Lymphocyte anti-gen Leu-19 as a molecular marker of regeneration in human skeletal muscle. *Proc Natl Acad Sci U S A* 86: 307-311, 1989.
267. Serrano AL, Baeza-Raja B, Perdiguero E, Jardi M and Munoz-Canoves P. Inter-leukin-6 is an essential regulator of satellite cell-mediated skeletal muscle hypertrophy. *Cell Metab* 7: 33-44, 2008.
268. Sewright KA, Hubal MJ, Kearns A, Holbrook MT and Clarkson PM. Sex differences in response to maximal eccentric exercise. *Med Sci Sports Exerc* 40: 242-251, 2008.
269. Sherman WM, Armstrong LE, Murray TM, Hagerman FC, Costill DL, Staron RC and Ivy JL. Effect of a 42.2-km footrace and subsequent rest or exercise on muscular strength and work capacity. *J Appl Physiol* 57: 1668-1673, 1984.
270. Shireman PK, Contreras-Shannon V, Ochoa O, Karia BP, Michalek JE and McManus LM. MCP-1 deficiency causes altered inflammation with impaired skeletal muscle regeneration. *J Leukoc Biol* 81: 775-785, 2007.
271. Sinert R, Kohl L, Rainone T and Scalea T. Exercise-induced rhabdomyolysis. *Ann Emerg Med* 23: 1301-1306, 1994.

272. Sjoström M, Friden J and Ekblom B. Endurance, what is it? Muscle morphology after an extremely long distance run. *Acta Physiol Scand* 130: 513-520, 1987.
273. Sjoström M, Johansson C and Lorentzon R. Muscle pathomorphology in m. quadriceps of marathon runners. Early signs of strain disease or functional adaptation? *Acta Physiol Scand* 132: 537-541, 1988.
274. Smith C, Kruger MJ, Smith RM and Myburgh KH. The inflammatory response to skeletal muscle injury: illuminating complexities. *Sports Med* 38: 947-969, 2008.
275. Smith LL. Acute inflammation: the underlying mechanism in delayed onset muscle soreness? *Med Sci Sports Exerc* 23: 542-551, 1991.
276. Smith LL, Anwar A, Fragen M, Rananto C, Johnson R and Holbert D. Cytokines and cell adhesion molecules associated with high-intensity eccentric exercise. *Eur J Appl Physiol* 82: 61-67, 2000.
277. Smith LL, McKune AJ, Semple SJ, Sibanda E, Steel H and Anderson R. Changes in serum cytokines after repeated bouts of downhill running. *Appl Physiol Nutr Metab* 32: 233-240, 2007.
278. Snijders T, Verdijk LB and van Loon LJ. The impact of sarcopenia and exercise training on skeletal muscle satellite cells. *Ageing Res Rev* 8: 328-338, 2009.
279. Soltow QA, Betters JL, Sellman JE, Lira VA, Long JH and Criswell DS. Ibuprofen inhibits skeletal muscle hypertrophy in rats. *Med Sci Sports Exerc* 38: 840-846, 2006.
280. Soricter S, Puschendorf B and Mair J. Skeletal muscle injury induced by eccentric muscle action: muscle proteins as markers of muscle fiber injury. *Exerc Immunol Rev* 5: 5-21, 1999.
281. Staron RS, Hikida RS, Murray TF, Nelson MM, Johnson P and Hagerman F. Assessment of skeletal muscle damage in successive biopsies from strength-trained and untrained men and women. *Eur J Appl Physiol Occup Physiol* 65: 258-264, 1992.
282. Stauber WT. Eccentric action of muscles: physiology, injury, and adaptation. *Exerc Sport Sci Rev* 17: 157-185, 1989.
283. Stauber WT, Clarkson PM, Fritz VK and Evans WJ. Extracellular matrix disruption and pain after eccentric muscle action. *J Appl Physiol* 69: 868-874, 1990.
284. Stauber WT and Smith CA. Cellular responses in exertion-induced skeletal muscle injury. *Mol Cell Biochem* 179: 189-196, 1998.
285. Steensberg A, Keller C, Starkie RL, Osada T, Febbraio MA and Pedersen BK. IL-6 and TNF- α expression in, and release from, contracting human skeletal muscle. *Am J Physiol Endocrinol Metab* 283: E1272-E1278, 2002.
286. Stupka N, Lowther S, Chorneyko K, Bourgeois JM, Hogben C and Tarnopolsky MA. Gender differences in muscle inflammation after eccentric exercise. *J Appl Physiol* 89: 2325-2332, 2000.
287. Stupka N, Tarnopolsky MA, Yardley NJ and Phillips SM. Cellular adaptation to repeated eccentric exercise-induced muscle damage. *J Appl Physiol* 91: 1669-1678, 2001.
288. Sudbo J, Reith A, Florenes VA, Nesland JM, Ristimäki A and Bryne M. COX-2 expression in striated muscle under physiological conditions. *Oral Dis* 9: 313-316, 2003.
289. Takekura H, Fujinami N, Nishizawa T, Ogasawara H and Kasuga N. Eccentric exercise-induced morphological changes in the membrane systems involved in excitation-contraction coupling in rat skeletal muscle. *J Physiol* 533: 571-583, 2001.

290. Talbot JA and Morgan DL. Quantitative analysis of sarcomere non-uniformities in active muscle following a stretch. *J Muscle Res Cell Motil* 17: 261-268, 1996.
291. Talbot JA and Morgan DL. The effects of stretch parameters on eccentric exercise-induced damage to toad skeletal muscle. *J Muscle Res Cell Motil* 19: 237-245, 1998.
292. Tee JC, Bosch AN and Lambert MI. Metabolic consequences of exercise-induced muscle damage. *Sports Med* 37: 827-836, 2007.
293. Testa M, Rocca B, Spath L, Ranelletti FO, Petrucci G, Ciabattini G, Naro F, Schiaffino S, Volpe M and Reggiani C. Expression and activity of cyclooxygenase isoforms in skeletal muscles and myocardium of humans and rodents. *J Appl Physiol* 103: 1412-1418, 2007.
294. Thompson D, Bailey DM, Hill J, Hurst T, Powell JR and Williams C. Prolonged vitamin C supplementation and recovery from eccentric exercise. *Eur J Appl Physiol* 92: 133-138, 2004.
295. Tidball JG. Inflammatory cell response to acute muscle injury. *Med Sci Sports Exerc* 27: 1022-1032, 1995.
296. Tidball JG. Inflammatory processes in muscle injury and repair. *Am J Physiol Regul Integr Comp Physiol* 288: R345-R353, 2005.
297. Toft AD, Jensen LB, Bruunsgaard H, Ibfelt T, Halkjaer-Kristensen J, Febbraio M and Pedersen BK. Cytokine response to eccentric exercise in young and elderly humans. *Am J Physiol Cell Physiol* 283: C289-C295, 2002.
298. Toumi H, F'guy S and Best TM. The role of neutrophils in injury and repair following muscle stretch. *J Anat* 208: 459-470, 2006.
299. Trappe TA, Carroll CC, Dickinson JM, LeMoine JK, Haus JM, Sullivan BE, Lee JD, Jemiolo B, Weinheimer EM and Hollon CJ. Influence of acetaminophen and ibuprofen on skeletal muscle adaptations to resistance exercise in older adults. *Am J Physiol Regul Integr Comp Physiol* 300: R655-R662, 2011.
300. Trappe TA, Fluckey JD, White F, Lambert CP and Evans WJ. Skeletal muscle PGF(2)(alpha) and PGE(2) in response to eccentric resistance exercise: influence of ibuprofen acetaminophen. *J Clin Endocrinol Metab* 86: 5067-5070, 2001.
301. Trappe TA, White F, Lambert CP, Cesar D, Hellerstein M and Evans WJ. Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis. *Am J Physiol Endocrinol Metab* 282: E551-E556, 2002.
302. Trappe TA, White F, Lambert CP, Cesar D, Hellerstein M and Evans WJ. Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis. *Am J Physiol Endocrinol Metab* 282: E551-E556, 2002.
303. Trenerry MK, Carey KA, Ward AC and Cameron-Smith D. STAT3 signaling is activated in human skeletal muscle following acute resistance exercise. *J Appl Physiol* 102: 1483-1489, 2007.
304. Trump BF, Laiho KA, Mergner WJ and Arstila AU. Studies on the subcellular pathophysiology of acute lethal cell injury. *Beitr Pathol* 152: 243-271, 1974.
305. Uchida MC, Nosaka K, Ugrinowitsch C, Yamashita A, Martins E Jr, Moriscot AS and Aoki MS. Effect of bench press exercise intensity on muscle soreness and inflammatory mediators. *J Sports Sci* 27: 499-507, 2009.
306. Vihko V, Rantamaki J and Salminen A. Exhaustive physical exercise and acid hydrolase activity in mouse skeletal muscle. A histochemical study. *Histochemistry* 57: 237-249, 1978.

307. Vihko V, Salminen A and Rantamaki J. Exhaustive exercise, endurance training, and acid hydrolase activity in skeletal muscle. *J Appl Physiol* 47: 43-50, 1979.
308. Vincent HK and Vincent KR. The effect of training status on the serum creatine kinase response, soreness and muscle function following resistance exercise. *Int J Sports Med* 18: 431-437, 1997.
309. Warden SJ. Cyclo-oxygenase-2 inhibitors : beneficial or detrimental for athletes with acute musculoskeletal injuries? *Sports Med* 35: 271-283, 2005.
310. Warhol MJ, Siegel AJ, Evans WJ and Silverman LM. Skeletal muscle injury and repair in marathon runners after competition. *Am J Pathol* 118: 331-339, 1985.
311. Warner DC, Schnepf G, Barrett MS, Dian D and Swigonski NL. Prevalence, attitudes, and behaviors related to the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in student athletes. *J Adolesc Health* 30: 150-153, 2002.
312. Warren GL, Hayes DA, Lowe DA and Armstrong RB. Mechanical factors in the initiation of eccentric contraction-induced injury in rat soleus muscle. *J Physiol* 464: 457-475, 1993.
313. Warren GL, Hulderman T, Jensen N, McKinstry M, Mishra M, Luster MI and Simeonova PP. Physiological role of tumor necrosis factor alpha in traumatic muscle injury. *FASEB J* 16: 1630-1632, 2002.
314. Warren GL, Hulderman T, Mishra D, Gao X, Millecchia L, O'farrell L, Kuziel WA and Simeonova PP. Chemokine receptor CCR2 involvement in skeletal muscle regeneration. *FASEB J* 19: 413-415, 2005.
315. Warren GL, Ingalls CP, Lowe DA and Armstrong RB. What mechanisms contribute to the strength loss that occurs during and in the recovery from skeletal muscle injury? *J Orthop Sports Phys Ther* 32: 58-64, 2002.
316. Warren GL, Lowe DA and Armstrong RB. Measurement tools used in the study of eccentric contraction-induced injury. *Sports Med* 27: 43-59, 1999.
317. Warren GL, O'farrell L, Summan M, Hulderman T, Mishra D, Luster MI, Kuziel WA and Simeonova PP. Role of CC chemokines in skeletal muscle functional restoration after injury. *Am J Physiol Cell Physiol* 286: C1031-C1036, 2004.
318. Weinheimer EM, Jemiolo B, Carroll CC, Harber MP, Haus JM, Burd NA, LeMoine JK, Trappe SW and Trappe TA. Resistance exercise and cyclooxygenase (COX) expression in human skeletal muscle: implications for COX-inhibiting drugs and protein synthesis. *Am J Physiol Regul Integr Comp Physiol* 292: R2241-R2248, 2007.
319. Wernbom M, Paulsen G, Nilsen TS, Hisdal J and Raastad T. Contractile function and sarcolemmal permeability after acute low-load resistance exercise with blood flow restriction. *Eur J Appl Physiol* 2011.
320. Widrick JJ, Costill DL, McConnell GK, Anderson DE, Pearson DR and Zachwieja JJ. Time course of glycogen accumulation after eccentric exercise. *J Appl Physiol* 72: 1999-2004, 1992.
321. Willems ME and Stauber WT. Performance of plantar flexor muscles with eccentric and isometric contractions in intact rats. *Med Sci Sports Exerc* 32: 1293-1299, 2000.
322. Willoughby DS, McFarlin B and Bois C. Interleukin-6 expression after repeated bouts of eccentric exercise. *Int J Sports Med* 24: 15-21, 2003.

- 323. Yamin C, Duarte JA, Oliveira JM, Amir O, Sagiv M, Eynon N, Sagiv M and Amir RE. IL6 (-174) and TNFA (-308) promoter polymorphisms are associated with systemic creatine kinase response to eccentric exercise. *Eur J Appl Physiol* 104: 579-586, 2008.
- 324. Yu JG, Carlsson L and Thornell LE. Evidence for myofibril remodeling as opposed to myofibril damage in human muscles with DOMS: an ultrastructural and immunoelectron microscopic study. *Histochem Cell Biol* 121: 219-227, 2004.
- 325. Yu JG, Furst DO and Thornell LE. The mode of myofibril remodelling in human skeletal muscle affected by DOMS induced by eccentric contractions. *Histochem Cell Biol* 119: 383-393, 2003.
- 326. Yu JG, Malm C and Thornell LE. Eccentric contractions leading to DOMS do not cause loss of desmin nor fibre necrosis in human muscle. *Histochem Cell Biol* 118: 29-34, 2002.
- 327. Zammit PS. All muscle satellite cells are equal, but are some more equal than others? *J Cell Sci* 121: 2975-2982, 2008.
- 328. Ziltener JL, Leal S and Fournier PE. Non-steroidal anti-inflammatory drugs for athletes: an update. *Ann Phys Rehabil Med* 53: 278, 2010.