HIGHLIGHTED TOPIC | Exercise and Inflammation

Exercise, MAPK, and NF-κB signaling in skeletal muscle

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Kramer HF, Goodyear LJ. Exercise, MAPK, and NF-κB signaling in skeletal muscle. J Appl Physiol 103: 388–395, 2007. doi:10.1152/japplphysiol.00085.2007.—Mitogen-activated protein kinases (MAPKs) and NF-κB are two major regulators of gene transcription and metabolism in response to oxidative, energetic, and mechanical stress in skeletal muscle. Chronic activation of these signaling pathways has been implicated in the development and perpetuation of various pathologies, such as diabetes and cachexia. However, both MAPK and NF-κB are also stimulated by exercise, which promotes improvements in fuel homeostasis and can prevent skeletal muscle atrophy. This review will first discuss the major MAPK signaling modules in skeletal muscle, their differential activation by exercise, and speculated functions on acute substrate metabolism and exercise-induced gene expression. Focus will then shift to examination of the NF-κB pathway, including its mechanism of activation by cellular stress and its putative mediation of exercise-stimulated adaptations in antioxidant status, tissue regeneration, and metabolism. Although limited, there is additional evidence to suggest cross talk between MAPK and NF-κB signals with exercise. The objectives herein are twofold: 1) to determine how and why exercise activates MAPK and NF-κB; and 2) to resolve their paradoxical activation during diseased and healthy conditions.

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CHRONIC INFLAMMATION AND METABOLIC dysregulation are prominent features of diabetes, cardiovascular disease, and cachexia. The pathological stress underlying these conditions triggers persistent flux through multiple intracellular signaling pathways that coordinately amplify the diseased state. As master regulators of gene expression, redox status, and metabolism, mitogen-activated protein kinases (MAPK) and NF-κB signals have been shown to couple cellular stress with an adaptive or maladaptive response in skeletal muscle. Evidence suggests that unrestrained signaling through these two pathways perpetuates insulin resistance and protein catabolism (75, 85). Therefore, both MAPK and NF-κB represent exciting targets for pharmacological interventions aimed at preventing or ameliorating diabetes and muscle wasting.

In contrast, acute physical exercise initiates a number of beneficial effects in skeletal muscle, including improvements in glucose homeostasis (40), lipid metabolism (8), and insulin sensitivity (26), all of which are especially important for individuals with diabetes (30). Chronic exercise training promotes skeletal muscle hypertrophy and can mitigate age-related sarcopenia and osteopenia (37). Paradoxically, exercise also potently activates MAPK and NF-κB signaling in skeletal muscle. This increase in MAPK and NF-κB activities during diseased and healthy states is actually a necessary response to chronic and intermittent stress, respectively. Sustained elevations in reactive oxygen species (ROS) and metabolic perturbations accompany diabetes and cachexia (6, 61). Contracting skeletal muscle also constitutes a transient source of ROS (7) and becomes hypermetabolic during and following exercise. Activation of MAPK and NF-κB pathways by exercise is associated with regulation of distinct gene clusters and divergent cellular functions. Whereas the MAPK family has been implicated in growth and differentiation (70), NF-κB is a major stimulator of inflammation and muscle protein turnover (12). Each signaling cascade may additionally confer adaptive alterations in glucose and lipid metabolism. The following review will first describe the effects of exercise on MAPK and NF-κB in skeletal muscle and subsequently determine their putative roles in mediating exercise-induced physiological processes. However, it is acknowledged that the paucity of existing data limits full characterization of their cellular functions.

EXERCISE AND MAPK ACTIVATION

The MAPK family of proteins is composed of four distinct signaling modules in skeletal muscle: 1) extracellular signal-regulated kinases (ERK) 1 and 2 (ERK1/2); 2) p38 MAPK; 3) c-Jun NH2-terminal kinases (JNK); and 4) ERK5 or big MAPK. These MAPK branches are stimulated by cytokines, growth factors, and cellular stress (24, 49). Exercise, itself an intermittent form of cellular stress, was first shown by our laboratory to activate ERK1/2, p38, and JNK pathways in rat skeletal muscle (29). In more recent work, the activity of these distinct MAPK signaling modules has been shown to be partially dependent on the type, duration, and intensity of the contractile stimulus. Although ERK5 and its upstream activa-
tor MAPK/ERK kinase 5 are abundantly expressed in skeletal muscle (100), its activity has not been sufficiently evaluated following exercise.

ERK1/2 is rapidly activated in rat and mouse models of exercise (20, 29, 58) and in situ contraction (52, 58, 74), as well as in both trained and untrained human skeletal muscle following acute submaximal cycling (86, 87, 97) and marathon running exercise (95). The magnitude of ERK1/2 phosphorylation during exercise correlates with the intensity of the protocol (87), and both endurance and resistance exercise (16, 46, 88) can increase ERK1/2 phosphorylation. One-legged cycling exercise produces increases in phospho-ERK1/2 in the exercised legs only, suggesting that phosphorylation is due to local rather than systemic factors (5, 86). In support of this finding, isolated rat (31, 72, 90–92) and mouse (33, 50) skeletal muscles stimulated to contract in vitro exhibit increases in ERK1/2 phosphorylation.

Treadmill exercise in rodents (29, 58) and cycling ergometry (86) and marathon running (10, 95) in humans also increase phosphorylation of p38 MAPK. As a separate signaling component of the MAPK network, p38 MAPK consists of four isoforms (p38α, p38β, p38δ, and p38γ) that are primarily activated during high-intensity muscle contractions (71, 91, 97), including unaccustomed resistance exercise in some (15, 46) but not all (88) studies. Like ERK1/2, p38 MAPK phosphorylation increases during contraction of isolated skeletal muscles, implying a local means of activation (11, 33, 78, 91). There is some evidence to suggest tissue-specific regulation of the p38 MAPK family with exercise. Whereas the p38α and p38β isoforms are ubiquitously expressed, p38δ mRNA is detected mainly in the lung and kidney (43), and the p38γ isoform is almost exclusively expressed in skeletal muscle (51). Moreover, in immune complex assays that discriminate between p38α and p38γ, only the p38γ isoform is activated by marathon running exercise (10). Since contraction of isolated rat skeletal muscles in vitro has also been shown to elicit p38α and p38β kinase activity (78), future research is needed to clarify the specific roles of p38 MAPK isoforms following exercise and muscle contraction.

Intense exercise protocols and/or those inducing muscular damage additionally stimulate signal transduction through the JNK pathway (3, 9–11, 25). JNK phosphorylation increases linearly with escalating levels of muscular contraction force (52). Therefore, total muscle tension rather than duration of the contraction stimulus appears to be the influential modulator of JNK activity (71). In summary, all three MAPK signaling modules are responsive to exercise; however, their mechanisms of activation (energetic/metabolic vs. mechanical) remain distinct. The pattern of MAPK signaling may have important implications in the various adaptations associated with exercise.

**PUTATIVE ROLES FOR MAPK ACTIVATION BY EXERCISE**

Exercise-induced increases in the activity of MAPK signals have been shown to phosphorylate substrates involved in carbohydrate and fat metabolism, cell proliferation, differentiation, hypertrophy, apoptosis, and inflammation, as well as transcription factors and coactivators (Fig. 1). This latter modulation of gene transcription may be especially important for the adaptive and/or plastic response of skeletal muscle to repeated bouts of exercise. Thus MAPK may fulfill an important function as a cellular intermediary coupling perceived alterations in stress with adaptive changes in 1) redox status, 2) fuel homeostasis, and 3) gene regulation.

**Oxidative Stress and MAPK Activation**

One putative role of exercise-stimulated MAPK activation is the transcriptional regulation of redox status in skeletal muscle. The mechanical and energetic perturbations associated with exercise result in immediate increases in ROS in skeletal muscle. Alterations in free radical concentration are rapidly sensed, neutralized, and accompanied by adaptive increases in oxidant buffering capacity through upregulation of key antioxidant enzymes. MAPK activity may partially mediate this response. Hydrogen peroxide (H_2O_2) induces strong activation of ERKs, JNKs, and p38 MAPK signaling modules in a dose- and time-dependent manner in skeletal myoblasts (47) and triggers phosphorylation of p38 MAPK and increases glucose transport in isolated skeletal muscle preparations (48, 82).

Selective inhibition of p38 MAPK substantially reduces the activation of glucose transport induced by the oxidative stress (48). Similarly, skeletal muscle contracted in the presence of the antioxidant N-acetylcysteine exhibit decreased rates of glucose transport, owing to the dampened production of ROS...
(73). All three major MAPK signaling modules appear to be activated by acute high-intensity exercise that significantly elevate muscle ROS. Interestingly, repeated exposure to this type of exercise (training) actually makes the organism more resistant to oxidative stress and may partially explain the attenuated response of exercise-induced MAPK activation in highly trained individuals (15, 97).

**Metabolic Actions of MAPK Activation**

Exercise promotes insulin-independent increases in glucose transport and fatty acid uptake and oxidation in contracting skeletal muscle. Acute exercise effects on glucose transport and glycogen synthesis are probably not mediated by ERK1/2, p38, or JNK (25, 89). Regulated contraction-stimulated glucose transport or glycogen synthesis without affecting glucose and glycogen synthesis are probably not mediated by ERK1/2, as inhibitors of MAPK/ERK kinase abolish contraction-stimulated ERK1/2 phosphorylation without affecting glucose transport (31, 90). Additional studies show that JNK does not regulate contraction-stimulated glucose transport or glycogen metabolism in skeletal muscle (25, 89).

In contrast, initial work using the p38α/β antagonist SB203580 suggested that p38 MAPK isoforms may partially regulate contraction-stimulated glucose transport in skeletal muscle (77). However, our laboratory has subsequently shown that SB203580 inhibits both insulin- and contraction-stimulated glucose transport independently of p38α or β activity (27). Other reports have demonstrated that SB203580 acts as a competitive inhibitor glucose transport through direct interaction with the glucose transporter (68) and that overexpression of dominant-negative p38 mutants in skeletal muscle does not affect glucose transport (2). Therefore, it is unlikely that p38α and p38β are significant regulators of exercise-stimulated glucose transport in skeletal muscle. In addition, although the p38y MAPK isoform is primarily expressed in skeletal muscle and is strongly regulated by acute exercise (10), overexpression of p38y actually decreases GLUT-4 expression and contraction-stimulated glucose transport (32). These data collectively suggest p38 MAPK signaling does not mediate acute increases in glucose transport following exercise.

In addition to its partitioning effects on glucose, exercise increases fatty acid uptake and oxidation in skeletal muscle. Several studies implicate ERK1/2 activity in various aspects of lipid metabolism, including regulation of acetyl-CoA carboxylase (67) and hormone-sensitive lipase (19) phosphorylation. ERK1/2 has specifically been shown to regulate fatty acid uptake during contraction in rat skeletal muscle, perhaps through membrane recruitment of the fatty acid binding protein CD36 (84). Recent data utilizing low-to-moderate exercise further suggest that increased fatty acid uptake and oxidation are ERK1/2 dependent in vivo (66). Collectively, these data support a role for MAPK modules in the metabolic alterations accompanying exercise.

**Gene Regulation**

MAPK can potentially modulate gene expression through at least two mechanisms: 1) phosphorylation of transcription factors and 2) chromatin remodeling. To date, numerous substrates of MAPK have been identified, including several transcription factors. JNK activation by skeletal muscle contraction is associated with a rapid increase in mRNA of the early response genes c-jun and c-fos (3, 4). These transcription factors are important regulators of cell proliferation, apoptosis, inflammation, and DNA repair (45), and their induction by exercise may augment muscle regeneration.

ERK1/2 directly phosphorylates mitogen- and stress-activated kinase 1 and 2, as well as p90 ribosomal S6 kinase. These proteins appear to alter the activity of the transcription factor cAMP response element-binding protein and Elk-1 and are phosphorylated in response to exercise (95). Interestingly, p38 MAPK can directly phosphorylate Elk-1 and another transcription factor, myocyte-enhancing factor (MEF) 2, in the nucleus of cultured cells without the need for an intermediary kinase (65, 93). Although MEF2 binding activity has been demonstrated to increase with exercise (53, 96), the link between p38 induction of MEF2 is still lacking. It is clear, however, that MEF2 activation by exercise is part of the mechanism whereby GLUT-4 expression is adaptively upregulated to enhance glucose transport (54).

Exercise training is associated with alterations that favor muscle oxidative capacity, including fiber-type transformation and mitochondrial biogenesis. The peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) has been implicated in these and other effects, and its mRNA expression is significantly increased by one bout of exercise concomitant with p38 MAPK phosphorylation (1, 14). Activation of the p38 MAPK pathway in cultured myocytes stimulates PGC-1α promoter activity through engagement of the downstream transcription factor activating transcription factor (ATF)-2. These effects are blocked by pharmacological inhibitors of p38, overexpression of dominant-negative p38, and overexpression of dominant-negative ATF-2, consistent with the idea that p38 MAPK signals through ATF-2 to induce expression of the PGC-1α gene in response to exercise (1).

Histone phosphorylation in the nucleus can modify chromatin structure and is, therefore, an alternate means of transcriptional regulation. Increases in histone H3 phosphorylation have been observed following intense exercise in humans (97), and MAPK signaling in response to multiple stimuli (38, 55) mediates rapid serine phosphorylation of histone H3. Although not a direct substrate of MAPK, histone H3 is a downstream target of p90 ribosomal S6 kinase (59) and mitogen- and stress-activated kinase 1 (81), which are both activated by exercise (95).

To summarize, MAPK signaling appears to be involved in the metabolic and mitogenic plasticity of skeletal muscle in response to exercise (Fig. 1). Future research should attempt to define specific roles for each MAPK pathway in these exercise-induced adaptations.

**NF-κB: MASTER CONTROLLER OF INFLAMMATION AND REDOX STATUS**

NF-κB lies at the nexus of multiple signaling pathways that orchestrate diverse processes in virtually every type of cell. As a nuclear transcription factor, NF-κB directly alters the production of over 150 genes, including those encoding cytokines, immune, and antigen-presenting receptors, and regulators of redox status, acute-phase response, apoptosis, cachexia and disuse atrophy, and host defense (63). The NF-κB/Rel family is composed of five members, including p50, p52, p65 (RelA), RelB, and c-Rel (18). Two of these proteins must dimerize to facilitate binding of NF-κB to DNA and gene regulation. Recent evidence suggests the p50-p65 heterodimer is respon-
sible for the majority of NF-kB activity in skeletal muscle (39). In unstimulated tissue, the nuclear localization sequence of NF-kB is bound to inhibitory IκB proteins, of which there are seven mammalian species, including IκBα, IκBβ, IκBε, IκBγ, Bcl-3, p100, and p105 (28). However, activation of IκBα kinase (IKK) by various stimuli results in IκB phosphorylation at serines 32 and 36, which initiates ubiquitination and subsequent IκB degradation via the proteosome (Fig. 2A). Only NF-κB complexes liberated from their IκB inhibitory proteins can translocate into the nucleus to impart their regulatory functions (18, 28).

Transgenic mice engineered to possess constitutive muscle-specific activation of IκB kinase β (MIKK) (Fig. 2B) exhibit profound sarcopenia, increased proteolysis, and an overall cachectic phenotype (12). Despite their nearly 15-fold increases in NF-κB activity, MIKK mice have normal levels of proinflammatory cytokines and show no overt insulin resistance. When MIKK mice are crossed with mice expressing a muscle-specific IκBα superrepressor (MISR) transgene (Fig. 2B), the accelerated protein catabolism is downregulated and muscle mass is restored, suggesting NF-κB is directly responsible for mediating the cachexia. Similarly, salicylate therapy in MIKK mice reverses the muscle-wasting effects of unrestrained NF-κB activity. High doses of these pharmacological compounds (e.g., 120 mg kg⁻¹day⁻¹) have been demonstrated to inhibit both IκB and NF-κB (94, 98) and significantly reduce NF-κB activity in MIKK mice.

Chronic activation of NF-κB is associated with various pathological conditions, including insulin resistance and muscle wasting. Human subjects with Type 2 diabetes exhibit decreased IκB protein abundance and increased activity of NF-κB in muscle that directly correlates with impaired insulin-mediated glucose disposal (80). Enduring hyperglycemia and/or extreme perturbations in glycemia are common generators of oxidative stress, which has been shown to induce insulin resistance through activity of NF-κB (61). Interestingly, administration of the common salicylate aspirin (7.0 g/day) in patients with Type 2 diabetes enhances glucose homeostasis and peripheral insulin sensitivity, at least in part through the inhibition of IκB and NF-κB nuclear activity (36). Targeted manipulation or ablation of NF-κB, therefore, remains at the forefront of innovative treatments for diabetes and inflammatory pathologies. However, activation of NF-κB may not always be contraindicated. As discussed in the next section, the acute bursts associated with exercise appear to be normal and even necessary for beneficial exercise-mediated adaptations.

EXERCISE AND NF-κB ACTIVATION

Exercise and muscle contractions stimulate sarcoplasmic calcium release, increase ROS, and activate numerous signaling cascades, including MAPK. In various cell models, increased intracellular calcium (35), ROS accumulation (44, 57), and MAPK activation (13, 99) have all been shown to activate NF-κB, leading to the hypothesis that exercise may also activate NF-κB. As of this review, the majority of publications have demonstrated that exercise enhances NF-κB activity at several nodes of the IκBα/NF-κB pathway (33, 34, 41, 42, 79), although one study reported a reduction in NF-κB nuclear binding activity after exercise (21).

Acute treadmill exercise increases IκKα/β phosphorylation, IκBα phosphorylation, and NF-κB activity in rat skeletal muscle (33, 34, 41, 42, 79). Whereas the phosphorylation of IκBα increases during exercise, NF-κB nuclear binding activ-
ity peaks in the postexercise interval (33, 41). Activation of NF-κB is a local event in contracting muscle, because it can occur in the absence of exercise-derived systemic factors (33). Pharmacological inhibitors of p38 and ERK1/2 are able to blunt contraction-mediated IKKα/β phosphorylation by 39 and 35%, respectively, and in combination by 76%, suggesting MAPK signaling may participate in local activation of NF-κB in skeletal muscle (33).

Chronic exercise training may also alter the composition and activity of the IkBa/NF-κB pathway. Twelve weeks of treadmill exercise training in rats resulted in significantly decreased IkBa protein and increased phosphorylation of IKK, suggesting that NF-κB activation was elevated after training. Training also increased suppressor of cytokine signaling-3 and IL-6 mRNA expression in both white (plantaris) and red (soleus) muscles, which may be direct targets of NF-κB (see below) (79). In contrast, healthy individuals and subjects with Type 2 diabetes exhibited increases in the NF-κB inhibitory proteins IkBa and IkBβ following a moderate exercise training program, which was associated with improvements in insulin-stimulated glucose disposal (80). Differences in NF-κB activity after training may reflect the nature (intensity, duration, and frequency) of the exercise performed and/or full recovery between successive bouts of exercise.

**PUTATIVE ROLES FOR NF-κB ACTIVATION BY EXERCISE**

The functions of exercise-stimulated increases in NF-κB activity are currently unknown. However, given the array of NF-κB-responsive gene products, it is tempting to speculate on at least three potential actions conferred at the transcriptional level of regulation (Fig. 3): 1) NF-κB may serve as one mechanism to counter oxidative stress; 2) NF-κB may induce a brief but important proinflammatory response critical for muscle regeneration postexercise; and 3) NF-κB activity may also lead to changes in skeletal muscle glucose transport, glycogen repletion, and lipid oxidation after exercise. These three functions will be explored in greater detail below.

**Oxidative Stress and NF-κB Activation**

During unaccustomed and/or heavy treadmill exercise, ROS are produced from several sites within myofibers and are amplified with concomitant exposure to proinflammatory cytokines TNF-α, IL-1, and IFN-γ (7, 17, 60). In mitochondria, superoxide production is increased through complexes I and III of the electron transport chain (7, 17). Superoxide is usually converted to H2O2 by manganese superoxide dismutase (MnSOD) and diffuses into the cytosol, where it has been shown to activate IKK. ROS are additionally produced in peroxisomes (catalase), cytosol (xanthine oxidase), and membranes (lipooxygenase and NADPH oxidase). NF-κB rapidly responds to ROS by increasing transcription of at least three important antioxidant genes, including MnSOD, inducible nitric oxide synthase, and γ-glutamylcysteine synthetase, each of which buffer increases in oxidative stress. Treadmill exercise in rats has been shown to enhance NF-κB binding to its corresponding DNA binding domain of the MnSOD gene in skeletal muscle, which is associated with robust increases in MnSOD protein content 48 h later (34). In addition, pyrroldine dithiocarbamate, an antioxidant inhibitor of NF-κB, partially blocks nuclear NF-κB binding and completely abolishes exercise-induced IkBa phosphorylation and degradation, as well as p50 nuclear content (41). Multiple studies in cells and other tissues have confirmed the ability of antioxidants to decrease or eliminate peroxide-stimulated NF-κB activity. Thus it is possible that increases in NF-κB activity following exercise are partially designed to make skeletal muscle more resistant to future bouts of oxidative stress.

**Muscle Damage and NF-κB Activation**

Another potential function for NF-κB following exercise consists of its classical induction of acute-phase proteins and proinflammatory genes to facilitate postexercise regenerative responses in damaged tissue. Indeed, skeletal muscle inflammation and increased protein turnover appear to be necessary for exercise-induced hypertrophic adaptations (22). Studies assessing the effects of the anti-inflammatory drugs ibuprofen and acetaminophen have found that over-the-counter doses suppress the protein synthetic response in skeletal muscle after eccentric resistance exercise (83), which may be detrimental to skeletal muscle growth. NF-κB and p38 MAPK directly regulate expression of various prostaglandins, including the cyclooxygenase enzymes targeted by these and other nonsteroidal anti-inflammatory drugs (63, 76). It is important to note that exercise-stimulated increases in skeletal muscle inflammation...
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Invited Review

The paradox revisited

Clearly, activation of MAPK and NF-κB during and following exercise is healthy and probably necessary for exercise-induced muscle plasticity. However, abnormal activities in certain diseases are part of an adaptive response that exacerbates the inflammatory and insulin-resistant condition (Fig. 3). This apparent paradox may be resolved by at least two explanations: timing and specificity. First, exercise causes brief but robust perturbations in cellular stress, including increases in ROS and metabolism that quickly stabilize postexercise. Diabetes and cachexia are chronic conditions of continual ROS production, inflammation, and hypermetabolism. Alternatively, distinct NF-κB complexes may be selectively activated by exercise compared with pathological conditions. NF-κB can exist as homodimers of p50 or p65, or as p50/p65 heterodimers, and each of these forms could be regulated and function differentially, depending on the stimulus (18).

SUMMARY

MAPK and NFκB signals are fundamental modulators of cellular stress. Both pathways are activated by exercise, although the onset of their activity is different and depends on the intensity and duration of exercise. Furthermore, each pathway is characterized by unique physiological effects, probably through differences in gene targets mediating redox status, inflammation, metabolism, and other processes associated with exercise. Future research should elaborate on the roles of NFκB and MAPK and their interactions, particularly in the context of episodic vs. chronic cellular stress.

REFERENCES


Fuel Metabolism and NF-κB Activation

NF-κB may also mediate alterations in fuel metabolism during and following exercise through increased transcription of the IL-6 gene. IL-6 has been shown to enhance glucose transport and lipid oxidation in muscle (64) and is directly produced in contracting skeletal muscle during prolonged exercise (62). Initial evidence in muscle cells suggests that activation of NFκB results in significant IL-6 expression (79). To date, however, no studies have determined whether contracting skeletal muscle requires NFκB for increased expression of IL-6 or its secretion into plasma.

INTEGRATION OF MAPK AND NFκB SIGNALING INPUTS FOLLOWING EXERCISE

It is likely that MAPK and NFκB activation act coordinately in the metabolic, inflammatory, and genetic consequences of exercise. Indeed, both MAPK and NFκB pathways participate in the response of skeletal myoblasts to oxidative stress (47). H2O2 strongly activates all three MAPK signaling modules (ERKs, JNKs, and p38) in a dose- and time-dependent manner. In addition, H2O2 increases phosphorylation of IkB, nuclear translocation of NFκB, and phosphorylation of p65. While selective inhibition of MAPK modules does not affect H2O2-induced NFκB nuclear localization, it does alter the phosphorylation status of p65, perhaps modulating signal specificity. Thus it appears that there may be limited cross talk between MAPK and NFκB pathways in response to oxidative stress in myoblasts (47). This may not be the case with exercise and muscle contraction. Evidence in skeletal muscles stimulated to contract in vitro suggests MAPKs are upstream of NFκB and can partially mediate contraction-stimulated NFκB activity (33). In addition, Ji et al. (42) speculate that integrated inputs from MAPK and NFκB signaling pathways are required to mediate gene expression of MnSOD and/or inducible nitric oxide synthase in skeletal muscle in response to exercise stress.

attenuate with chronic training (69). This further validates the utility of episodic NFκB activity as a beneficial mediator of exercise-induced adaptations to cellular stress.

In contrast, muscle-specific ablation of IKKβ in mice was recently reported to protect against denervation-induced proteolysis and muscle atrophy and promoted improvements in muscle regenerative capacity following cardiotoxin injection (56). Although this suggests a negative role for NFκB on healing from acute muscle injury, the results must be interpreted cautiously, particularly in the context of exercise. Both denervation and cardiotoxin are extreme neuromuscular insults, while exercise is a milder perturbation affecting multiple systems. In addition, depletion of IKKβ might result in NFκB-independent effects in the nucleus, as the IKK pathway has been shown to directly phosphorylate nuclear histone H3 and various co-repressors (23). Future studies are needed to elucidate how IKKβ and/or its ablation influence exercise-stimulated adaptations.
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