Published in final edited form as:

Exp Physiol. 2013 January ; 98(1): 19–24. doi:10.1113/expphysiol.2011.063321.

NF-kappaB signaling and transcriptional regulation in skeletal muscle atrophy

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Abstract

The NF-kappaB signaling pathway is a necessary component of adult skeletal muscle atrophy due to systemic illnesses or disuse. Studies showing a role for the NF-kappaB pathway in muscle disuse focus on unloading, denervation, or immobilization, and studies showing a role for NF-kappaB in systemic illnesses include cancer, chronic heart failure, and acute septic lung injury. Muscle atrophy due to most of these triggers is associated with activation of NF-kappaB transcriptional activity. With the exception of muscle unloading however, there is a paucity of data on the NF-kappaB transcription factors that regulate muscle atrophy and there little known about which genes are targeted by NF-kappaB transcription factors during atrophy. Interestingly, in some cases it appears that the amelioration of muscle atrophy by genetic inhibition of NF-kappaB signaling proteins is due to effects that are independent of the downstream NF-kappaB transcription factors. These questions are prime areas for investigation if we are to understand a key component of muscle wasting in adult skeletal muscle.

Distinguishing NF-kappaB signaling pathway vs. NF-kappaB-dependent transcription in adult skeletal muscle atrophy

The focus of this review is on the role of the nuclear factor-kappaB (NF- κ B) signaling pathway and NF- κ B transcriptional regulation of adult skeletal muscle atrophy due to disuse and systemic illnesses. The roles of NF- κ B signaling and NF- κ B transcriptional control of myogenesis and of primary muscle diseases are dealt with in recent excellent reviews (Peterson *et al.*, 2011; Peterson & Guttridge, 2008; Li *et al.*, 2008; Bakkar & Guttridge, 2010). Because of the brevity of the present review, the reader is directed to a recent thorough review for detail on known proteins involved with NF- κ B signaling, members of NF- κ B/Rel transcription factor family, and canonical and non-canonical pathways (Hayden & Ghosh, 2012). We shall use the term “NF- κ B signaling proteins” to refer to the (predominately) cytosolic proteins that regulate NF- κ B transcription factor activation and/or nuclear localization. These proteins include the inhibitor of kappaB (I κ B) kinases (IKK α and IKK β) and their regulatory protein the NF- κ B essential modulator (NEMO/IKK γ), NF- κ B inducing kinase (NIK), and the I κ B family of proteins. IKK α and IKK β can phosphorylate I κ B proteins leading to the transport of NF- κ B transcription factors to the nucleus.

In order to determine the role of NF- κ B signaling proteins in atrophy, investigators have knocked out or overexpressed dominant negative (d.n.) forms of these proteins and then have assessed the effect on the progression of atrophy. To determine if blocking NF- κ B signaling also blocks NF- κ B-dependent transcription, investigators have measured NF- κ B-dependent transcriptional activation, NF- κ B-DNA binding, or the requirement of NF- κ B

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transcription factors. Figure 1 illustrates the separation of the signaling and transcription regulating components of the NF- κ B system. External stimuli (triggers) activate the signaling components in the cytoplasm which then transmit this information to the nucleus by phosphorylating and removing regulatory molecules that retain the active transcriptional components in the cytoplasm. The triggers for atrophy due to systemic illness involve immune modulators, especially catabolic cytokines such as TNF α (Bonetto *et al.*, 2012; Ladner *et al.*, 2003; Acharyya *et al.*, 2004; Yamaki *et al.*, 2012). The triggering stimulus of disuse atrophy is not known but it does not appear to involve immune activation (Frenette *et al.*, 2000; Hunter *et al.*, 2002). The triggers for disuse atrophy have not been linked to NF- κ B at this time, but two areas, mechanical tension in muscle and the oxidative state of muscle cells are currently being considered in this role (Goodman *et al.*, 2011; Powers *et al.*, 2012). The figure illustrates the canonical pathway which is mediated by IKK α , β , γ , regulating the activation of p65:p50 dimers, and it illustrates the pathway that we have found active in unloading atrophy in which upstream triggers activate p50 and Bcl-3, and perhaps IKK α and IKK β .

NF- κ B signaling is required for disuse and illness types of muscle atrophy

Work from several laboratories has shown that blocking NF- κ B signaling proteins attenuates muscle atrophy elicited by several different triggers. The muscle specific knockout of IKK β in mice ameliorated denervation atrophy by approximately 40% in gastrocnemius muscles based on fiber cross sectional area (Mourkioti *et al.*, 2006). Similarly, overexpression of the super repressor (SR) form of I κ B α in muscle of transgenic mice blocked denervation atrophy by 50% in gastrocnemius muscles (Cai *et al.*, 2004). Skeletal muscle atrophy in tumor bearing mice (the Lewis lung carcinoma line) was attenuated by 45% in the same transgenic mice overexpressing I κ B α -SR (Cai *et al.*, 2004). Muscle fiber atrophy from acute lung injury 2 days after intratracheal LPS infusion was abolished in the diaphragm of I κ B α -SR mice (Haegens *et al.*, 2012) while others showed the loss of gastrocnemius muscle mass was attenuated by 40%, 2 days after intratracheal LPS infused I κ B α -SR mice (Langen *et al.*, 2012). Similar to these studies, our lab showed that overexpression of the I κ B α -SR by plasmid injection in adult rat soleus muscles attenuated unloading-induced atrophy by 42% (Judge *et al.*, 2007). In addition, overexpression of either d.n. IKK β or d.n. IKK α in adult rat soleus muscle inhibited unloading-induced atrophy by 50% (Van Gammeren *et al.*, 2009). Overexpression of d.n. IKK β also blocked immobilization atrophy in rats by 50% (Reed *et al.*, 2011). Thus, IKK β and I κ B α are required signaling proteins for muscle atrophy due to inactivity and systemic illness triggers (Figure 1). IKK α is required for disuse atrophy but it is not yet known if it is required for illness-induced atrophy. Overexpression of c.a. IKK β (Cai *et al.*, 2004; Van Gammeren *et al.*, 2009) and c.a. IKK α (Van Gammeren *et al.*, 2009) caused significant muscle fiber atrophy showing that each of these kinases are sufficient to induce an atrophy phenotype in rat and mouse muscle. Taken together these data show that knockout or overexpression of d.n. NF- κ B signaling proteins using transgenic mice, or overexpression of d.n. forms of these proteins by plasmid injection all show the same results in different types of atrophy in rats and mice: that NF- κ B signaling is required for the progression of illness and disuse muscle atrophy.

Activation of NF- κ B-dependent transcription during different types of muscle atrophy

Since inhibition of NF- κ B signaling proteins can block several different types of muscle atrophy, a next logical question is whether this is achieved by blocking transcriptional activation via NF- κ B transcription factors. A valuable method to test if NF- κ B mediated transcriptional activity is decreased in cases where NF- κ B signaling is blocked is the use of

a NF- κ B-dependent reporter construct. During hindlimb unloading or cast immobilization of rats, NF- κ B-dependent reporter activity in the soleus increases 4 to 10-fold, but overexpression of d.n. IKK α , d.n. IKK β , or I κ B α -SR abolishes the increase in NF- κ B-dependent reporter activity (Senf *et al.*, 2008; Van Gammeren *et al.*, 2009; Judge *et al.*, 2007). Denervation of hindlimb muscle in WT mice showed a marked increase in the amount of protein bound to an NF- κ B oligonucleotide, but in IKK β knockout mice the protein-DNA binding due to denervation was almost as robust as the WT (Mourkioti *et al.*, 2006). In other work, atrophied muscles from denervated or LLC tumor-bearing mice showed increased protein binding to an NF- κ B oligo (using an ELISA assay format), and this increase in binding was strongly reversed when the I κ B α -SR was overexpressed (Cai *et al.*, 2004). During acute lung injury-induced muscle atrophy, NF- κ B-dependent reporter activity increases 2-fold, but it is not known whether I κ B α -SR reverses this activity (Haegens *et al.*, 2012). In a study on humans with chronic heart failure, nuclear protein from muscle biopsies show greatly increased binding of protein to an NF- κ B oligo, by gel shift assay, compared to healthy controls (Adams *et al.*, 2003).

Importance of the complete evaluation of NF- κ B protein transactivation

It is clear that blocking NF- κ B signaling proteins ameliorates many types of muscle atrophy, but it is difficult to determine whether this occurs by inhibition of NF- κ B transcriptional activation unless one uses a gel shift assay, and ideally, an NF- κ B-dependent reporter construct to measure in vivo NF- κ B activity. Even when using a reporter, we do not know which dimers, made from the 5 known mammalian NF- κ B transcription factors, are involved in regulating muscle atrophy. These factors and their transcriptional co-activators (e.g., Bcl-3, I κ B ζ , p300, etc.) are difficult to identify especially in whole muscle.

Identification of NF- κ B/I κ B transcription factors required for muscle atrophy

We have carried out several experiments in order to identify the NF- κ B transcription factors that are controlling the robust NF- κ B reporter activation during unloading atrophy. Initially we determined that p50, c-Rel, and Bcl-3 levels were increased in muscle nuclei during unloading and thus may be involved in driving NF- κ B reporter activity (Hunter *et al.*, 2002). Using knockout mice for each of these 3 proteins, we first showed that 100% of the NF- κ B reporter activity due to unloading in muscle was lost in *nfk1^{-/-}* (encodes p50) and in *bcl3^{-/-}* mice, and that atrophy was at least 70% blocked in *nfk1^{-/-}* and in *bcl3^{-/-}* mice (Hunter & Kandarian, 2004). Atrophy was not blocked in *rel^{-/-}* mice (Judge *et al.*, 2007). Bcl-3 is an I κ B protein that can bind p50 homodimers and can act as a co-transactivator (Bours *et al.*, 1993; Brasier *et al.*, 2001; Fujita *et al.*, 1993; Heissmeyer *et al.*, 1999). Thus we had identified two NF- κ B/I κ B transcriptional proteins that are required for disuse atrophy. When we take into consideration that blocking IKK α , IKK β or I κ B α signaling completely inhibited unloading-induced NF- κ B activity and inhibited atrophy by ~50%, we surmise that these dominant negative signaling proteins either inhibited the nuclear translocation of p50 and/or Bcl-3, or they are inhibiting the p50 component of the classical pathway, in turn having an effect on p50:Bcl-3 complexes (Figure 1).

Mechanical ventilation triggers diaphragm atrophy and is another model of unloading-induced atrophy. Pharmacological blockade of p50 (SN50) in mechanically ventilated rats reverses atrophy in Type I, IIa and IIx fibers and reverses the increase in nuclear p50-NF- κ B oligo binding (Smuder *et al.*, 2012). Other data to identify the transcription factors involved in NF- κ B signaling during muscle atrophy was the use of an ELISA assay for protein binding to an NF- κ B oligo followed by incubation with anti-p65. The authors used results from this assay to show an increase in NF- κ B binding activity in muscle during denervation

and tumor-induced wasting which was reversed in the presence of the I κ B α -SR as mentioned above (Cai *et al.*, 2004). These data suggest activation of the classical NF- κ B pathway, but additional assays are needed to confirm the involvement of p65.

NF- κ B signaling and NF- κ B transcriptional activity are not always tightly linked

While blocking NF- κ B signaling proteins significantly inhibits atrophy, in some cases, the atrophy is associated with little to no change in NF- κ B-dependent reporter activity. In our hands, atrophy associated with C-26 tumor bearing mice shows such results. We found no increase in NF- κ B-mediated gene transcription by a reporter, yet blocking NF- κ B signaling by overexpression of d.n. IKK β attenuated atrophy by 68%, (unpublished data). In this same type of muscle wasting, others have shown only a moderate (~30%) increase in NF- κ B DNA binding activity assessed by a gel shift assay (Shadfar *et al.*, 2011; Acharyya *et al.*, 2005). A similar sort of disconnection between NF- κ B intracellular signaling and nuclear activity is found in the marked denervation-induced increase in NF- κ B binding activity which was only slightly reversed in IKK β knockout mice (Mourkioti *et al.*, 2006). It is entirely possible that blocking NF- κ B signaling proteins could be blocking other cellular processes that in turn control atrophy but are not directly dependent on NF- κ B transcription factor mediated transcription. In the case of IKK inhibition, it is possible that blocking phosphorylation of other substrates besides I κ B α could cause a change in muscle fiber physiology. Recent work has shown that the IKKs have other protein substrates besides I κ B α and Rel proteins; examples include but are not limited to CBP, mTOR, FOXO, ERK1/2, histones, β -catenin, p53 and lysosomal proteins and these functions are NF- κ B-independent. For reviews on these important functions of the IKKs see Chariot (Chariot, 2009), Perkins (Perkins, 2007), Oeckinghaus *et al.* (Oeckinghaus *et al.*, 2011) or www.nf-kb.org, a comprehensive NF- κ B site created and maintained by the Gilmore lab. Some of the pathways affected by these non-NF- κ B functions of the IKKs are depicted in Figure 2. Since IKK α and IKK β are kinases, they are presumed to activate or inhibit their non-NF- κ B substrates via phosphorylation. For instance, phosphorylation of Foxo3 or β -catenin by IKK β deactivates Foxo- and β -catenin-dependent transcription, respectively, while IKK β phosphorylation of TSC1 activates the mTOR pathway (Chariot, 2009). In addition to the reviews, recent identification of the action of both IKKs to induce autophagy comes from two labs (Criollo *et al.*, 2010; Comb *et al.*, 2011).

It is also possible that NF- κ B transcription factors are required for regulation of atrophy genes in cases where there is a lack of increase in NF- κ B-dependent transcription. In this scenario, additional transcription factors are necessary and show increased cellular activation reflected by increased reporter activity during atrophy. Despite the overall control of the induction by the other transcription factor/s, a basal or constitutive level of NF- κ B binding may be required to upregulate certain atrophy genes. In this case, if basal NF- κ B binding to DNA were blocked, because of overexpression of the I κ B α -SR for instance, it would also block the upregulation of atrophy genes even though the normally inducing transcription factors are still upregulated.

Identification of NF- κ B target genes during atrophy

The final analysis in the study of the links between NF- κ B signaling, transcriptional activation and atrophy is the identification of the target genes that carry out the muscle wasting processes. The identification of NF- κ B target genes was undertaken, using *nfkb1*^{-/-}, *bcl3*^{-/-}, and wild type mice and comparing results from weight bearing vs. unloaded muscles for global gene expression (Wu *et al.*, 2011). Upregulated genes in wild type mice that are not upregulated in knockout mice were considered p50 or Bcl-3 target

genes. Interestingly, all genes that were p50 targets were also Bcl-3 targets suggesting that p50 and Bcl-3 may act in a complex to regulate unloading induced gene expression, as previously shown in other cell types (Bours *et al.*, 1993; Brasier *et al.*, 2001; Fujita *et al.*, 1993; Heissmeyer *et al.*, 1999). However, there were more Bcl-3 targets than p50 targets, suggesting that Bcl-3 may also induce chromatin transcription in complexes containing other DNA binding factors. Chromatin immunoprecipitation (ChIP) using antibodies to p50 and Bcl-3 confirmed selected atrophy genes as targets; signals reflecting p50 binding did not change with unloading but signals reflecting Bcl-3 (the transcriptional co-activator) binding increased at the same sites. Nearly complete are experiments using ChIP-sequencing in order to identify all the genes that are targets of p50 and Bcl-3 during muscle unloading. This will tell us, on a genome-wide basis, which genes are controlling the disuse atrophy process depend on p50 or Bcl-3 binding. Besides this line of experimentation, there is a dearth of published data on the NF- κ B transcription factors that are responsible for the different types of atrophy in adult muscle, even in experiments where blocking NF- κ B signaling showed attenuation of atrophy.

Summary and Future Directions

While it has been shown that inhibition of NF- κ B signaling attenuates approximately 50% of the atrophy triggered by disuse or by cancer, much remains to be understood. The downstream NF- κ B transcription factors required have only been identified for unloading atrophy. Further, identification of the genes targeted by NF- κ B signaling during the atrophy process in systemic illness is needed. The possibility of NF- κ B signaling inducing atrophy processes independent of NF- κ B transcription factors is also an important area for investigation. Finally, the understanding of NF- κ B transcriptional control of atrophy genes will ultimately need to be integrated with the other signaling and transcription factors which work in conjunction to produce the atrophied phenotype in different types of skeletal muscle loss.

Acknowledgments

This work was supported by NIH grants AR041705 and AR060217

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Topic of Review

- An up-to-date analysis on the role of NF-kappaB in adult skeletal muscle atrophy

Advances highlighted

- Our analysis of the literature and research in our lab has allowed us to propose interpretations that have not previously been published. We believe these interpretations will be of interest to scientists studying the cellular control of adult skeletal muscle atrophy.

Figure 1.

Schematic diagram showing NF-κB signaling and transcription factors involved in muscle atrophy due to illness or to disuse. NF-κB signaling proteins are involved in the signal transduction for atrophy from the myofiber membrane and/or external milieu to activate NF-κB transcription factors which then translocate to the nucleus and bind to NF-κB responsive elements (RE) and induce atrophy gene expression. Unloading atrophy seems to involve, IKKα and IKKβ, plus a non-classical complex involving p50 and Bcl-3. NF-κB signaling proteins are red. Transcription factors p65, p50, and Bcl-3 are green, yellow, and blue, respectively.

Figure 2.

Diagram showing the non-NF- κ B functions of IKK α (Left panel) and IKK β (Right panel). The two centrally depicted kinases act on a variety of substrates shown by either an arrow (substrate activated by kinase) or a “T” bar (substrate inhibited by kinase). The cellular processes affected are highlighted in an oval; yellow backgrounds are processes that are induced and blue backgrounds are processes that are inhibited by the kinase activity. Also noted are cases in where the kinase has activity inside the nucleus. The references for data in this figure are noted in the text. As can be surmised, there are several opportunities for each kinase to produce effects on muscle cell metabolism that may be independent of NF- κ B transcriptional activity.