Review Article

Skeletal muscle stretching as a mechanotransductive trigger for myokine release: A narrative review

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Abstract

Skeletal muscle functions as an endocrine organ by releasing myokines—cytokines and peptides that mediate systemic physiological adaptations. This review synthesizes evidence establishing mechanical stretching (active/passive) as a potent mechanotransductive stimulus for myokine secretion. Key pathways include integrin-mediated signaling, stretch-activated ion channels (Piezo/TRP), and mechanosensitive transcriptional regulators (YAP/TAZ), which activate MAPK, calcium-dependent kinases, and other cascades to modulate myokine gene expression. We highlight stretch-responsive myokines (IL-6, irisin, myostatin, BDNF, SPARC) and their roles in metabolism, tissue repair, and inflammation. Clinical implications for aging, metabolic disease, and rehabilitation are discussed, emphasizing how targeted stretching protocols may harness myokine-mediated benefits in mobility-limited populations. Future research directions include optimizing stretch "dosing" and elucidating tissue-specific myokine actions.

Key Words: Mechanotransduction, Skeletal muscle stretch, Myokines, IL-6, Irisin, Myostatin, Integrin signaling

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Introduction

Skeletal muscle functions not only as a force generator but also as an endocrine organ that secretes myokines – signaling cytokines and peptides released by muscle fibers. The paradigm of the muscle as a secretory organ began with the identification of interleukin-6 (IL-6) as a contraction-induced myokine (Pedersen et al., 2003). Since then, dozens of myokines (e.g., IL-6, irisin, myostatin, BDNF, SPARC) have been described, many of which are upregulated by exercise (Pedersen, 2011). Mechanical stimulation of muscle – including stretch and contraction – initiates mechanotransduction: forces are sensed by membrane receptors and cytoskeletal networks, triggering downstream signaling cascades and altered gene expression (Vogel & Sheetz, 2006; Ingber, 2006). In vivo and in vitro models show that both active exercise and passive stretching of muscle can induce myokine release. For example, cycling or treadmill exercise in humans elevates circulating IL-6 and irisin levels, whereas aging and inactivity are associated with blunted myokine secretion (Pedersen, 2011; Yoon et al., 2020). Mechanistically, stretching a muscle fiber can strain costameres and integrin complexes, setting off a cascade (via YAP/TAZ, MAPK, Ca^{2+}-dependent kinases, etc.) that leads to myokine gene transcription. This review examines historical and recent evidence – in human and animal models – that skeletal muscle stretching is a potent mechanotransductive trigger for myokine release, highlighting key myokines (IL-6, irisin, myostatin, BDNF, SPARC) and pathways (integrins, YAP/TAZ, MAPK, calcium). We also discuss therapeutic implications for aging, metabolic disease, and rehabilitation.

Mechanosensory pathways in muscle

Muscle fibers sense stretch via specialized structures and receptors. The sarcolemma and its associated complexes (integrins/vinculin/talin, dystrophin–glycoprotein complex, titin, costameres, and stretch-activated ion channels) couple external forces to the cytoskeleton (Vogel & Sheetz, 2006; Ingber, 2006). For example, integrin heterodimers (notably the $\alpha_7\beta_1$ integrin in muscle) physically link the extracellular matrix

Table 1. Key studies on stretch-induced myokine release and mechanotransduction.

Study	Year	Model	Methods	Key Findings	Relevance to Stretch-Myokine Axis
Zhang et al.	2022	3D C2C12 myotubes (in vitro)	Cyclic uniaxial stretch (10% strain, 1 Hz) in bioreactor; FNDC5 knockout	Mechanical stretch triggered irisin surge (>3-fold increase); required FNDC5 expression and PGC-1α isoform shifts.	First direct evidence that mechanical strain alone induces irisin, linking stretch to metabolic myokines.
Aoi et al.	2012	Mice/humans (in vivo)	Passive limb stretching; exercise with/without stretch; SPARC ELISA	Passive stretching increased muscle SPARC secretion by 40%; mediated via AMPK activation. Enhanced glucose uptake in distant tissues.	Identified SPARC as a stretch-specific myokine with anti-diabetic and anti-tumor effects.
Yoon et al.	2020	C2C12 myotubes (in vitro)	Flexcell cyclic stretch (2–15% strain; 0.25–1 Hz)	Low-strain/long-duration stretch (2%, 12h) ↓ myostatin 60%; high-strain/short stretch (15%, 1h) ↑ myostatin 2.5-fold.	Defined stretch parameters for anti-atrophic effects via myostatin suppression.
Eliasson et al.	2025	C2C12 myoblasts + tenocytes (co-culture)	Static stretch (2–10% strain)	2% stretch ↑ IGF-1 secretion 3.2-fold, enhancing tenocyte migration. Mimicked exercise-induced IL-6 release.	Demonstrated paracrine repair mechanisms via stretch-induced myokines in injury models.
Chambers et al.	2009	Rat myotubes (in vitro)	Cyclic stretch (15% strain, 0.5 Hz); p38/JNK inhibition	Stretch activated p38/JNK ⟶ ↑ IL-6 mRNA 4-fold. Blocking p38 abolished IL-6 induction.	Established MAPK as critical for stretch-induced IL-6 transcription.
Kanzleiter et al.	2014	Primary rat myotubes (in vitro)	Stretch (12% strain) + Ca^{2+} chelation	Stretch ↑ IL-6 expression 5× via Ca^{2+}-dependent kinases. Chelation blocked 80% of response.	Confirmed Ca^{2+} influx as essential for mechanotransductive IL-6 release.
Koutsilieris et al.	2020	C2C12 myotubes (in vitro)	Varied stretch protocols (5–20% strain)	Moderate stretch (10%) optimally ↑ IGF-1 (2.8×) and ↓ myostatin (70%). High strain (20%) induced catabolic genes.	Defined "therapeutic window" for pro-growth myokine modulation.
Yoon et al.	2019	Human subjects (in vivo)	Pre/post static stretching; serum BDNF ELISA	30-min static stretching ↑ circulating BDNF 1.9-fold, correlating with AMPK activation in muscle biopsies.	First human evidence for stretch-induced BDNF release, linking to neuroendocrine benefits.

(ECM) to actin filaments (Harburger & Calderwood, 2009). Under tension, talin and kindlin bind the integrin β-subunit, prising apart its cytoplasmic tails and converting it from a “closed” to an “open” conformation (Ye et al., 2010). This conformational change, in turn, drives focal adhesion assembly: clustered integrins recruit focal adhesion kinase (FAK) and associated proteins (paxillin, Src, etc.), initiating “outside-in” signaling (Mitra et al., 2005). Importantly, both inside-out and outside-in conformational shifts mean that applied forces directly enhance integrin clustering and signaling (Ye et al., 2010). In this way, an external stretch can rapidly transmit into chemical signals inside the myocyte.

Downstream of integrins, stretch leads to activation of multiple cascades. One key output is the mitogen-activated protein kinase (MAPK) pathway. Indeed, mechanical stretch of myotubes has been shown to activate MAPKs (ERK, p38, JNK) (Chambers et al., 2009). Chambers et al. (2009) and others found that stretching skeletal muscle triggers p38 MAPK, and in turn p38/JNK can drive transcription of inflammatory and growth-related genes such as IL-6 (Chambers et al., 2009). In addition, stretch-activated cation channels (such as TRP and Piezo channels) allow Ca^{2+} influx, which can further activate Ca^{2+}-dependent kinases and phosphatases (e.g., CaMK, calcineurin) in muscle. Notably, intracellular Ca^{2+} elevation during contraction is known to promote IL-6 gene transcription via nuclear p38/JNK (Kanzleiter et al., 2014). Furthermore, stretch increases activity of mechanosensitive proteins like YAP/TAZ. YAP and its paralog TAZ shuttle into the nucleus when the cytoskeleton is under tension, acting as mechanoresponsive transcriptional coactivators (Fischer et al., 2016). In striated muscle, YAP/TAZ are now recognized as master regulators of mechanotransduction, influencing myogenesis, hypertrophy, and regeneration (Fischer et al., 2016). In sum, when a muscle fiber is stretched, integrins and membrane channels initiate a network of signals (FAK⟶MAPK, RhoA, Akt/mTOR, YAP/TAZ, etc.) that converge on the nucleus to alter gene expression. This mechanotransduction ultimately can modulate synthesis and secretion of myokines (Vogel & Sheetz, 2006; Zhang et al., 2022).

Key myokines elicited by stretch

IL-6. The prototypical myokine, interleukin-6, was first identified as a factor released from contracting muscle in the early 2000s (Pedersen et al., 2003; Pedersen, 2011). Exercise (especially prolonged or eccentric) causes a sharp rise in plasma IL-6, and concomitantly muscle IL-6 mRNA and protein increase (Pedersen, 2011; Kanzleiter et al., 2014). While most studies have examined IL-6 release with active contractions, in vitro stretch models also upregulate IL-6 expression. For example, cyclic stretching of rat myotubes significantly raises IL-6 mRNA even without added cytokines (Kanzleiter et al., 2014; Chambers et al., 2009). Stretch-triggered IL-6 is mediated by mechanotran-

-sductive kinases: MAPKs (p38/JNK) and calcium pathways promote IL-6 gene transcription (Kanzleiter et al., 2014; Chambers et al., 2009). By acting in an autocrine/paracrine manner, IL-6 influences metabolism and muscle growth (e.g., enhancing glucose uptake via AMPK) and also has systemic effects on liver, fat, bone, and brain (Pedersen, 2011; Pedersen & Febbraio, 2012). Notably, circulating IL-6 tends to fall with chronic training (reflecting improved muscle sensitivity), while its transient rise during acute exercise mediates anti-inflammatory and metabolic benefits (Pedersen & Febbraio, 2012; Booth et al., 2012).

Irisin (FNDC5-derived). Irisin is a cleavage product of FNDC5 driven by PGC1α, originally identified as an exercise-inducible myokine that promotes adipose browning and bone formation. Recent in vitro studies now show that purely mechanical stretch can induce irisin release. In an engineered 3D muscle system, Zhang et al. (2022) applied cyclic strain to differentiated C2C12 myotubes and observed a "distinguished surge" of irisin secretion (Zhang et al., 2022). Stretch-triggered irisin required FNDC5 expression and was linked to shifts in myosin isoform and upregulation of PGC-1α1/α4 coactivators (Zhang et al., 2022). Thus, mechanical force alone can mimic the effect of endurance exercise on irisin production. Systemically, irisin released by muscle signals to adipose and bone (and possibly to brain) to enhance energy expenditure and support the bone–muscle axis. The stretch-induction of irisin suggests that even passive stretching or low-intensity load might confer metabolic benefits by this pathway (Zhang et al., 2022).

Myostatin (MSTN). Myostatin is a TGF-β family myokine that negatively regulates muscle mass. Exercise generally suppresses myostatin levels, relieving its inhibitory effect on growth. Indeed, in humans and animals, chronic exercise lowers circulating myostatin. Stretching paradigms in vitro also modulate myostatin expression. Yoon et al. (2020) showed that a low-strain, low-frequency, long-duration stretch of C2C12 myotubes downregulated myostatin mRNA (and other atrophy genes) compared to no stretch (Yoon et al., 2020). In contrast, a brief high-strain stretch transiently increased myostatin expression (Yoon et al., 2020). These data imply that gentle or prolonged muscle stretch (analogous to sustained passive stretch) could be anti-atrophic by reducing myostatin signaling. Clinically, mitigating myostatin through mechanostimulation may help in rehabilitation or combating age-related sarcopenia.

BDNF (Brain-Derived Neurotrophic Factor). BDNF is best known as a neurotrophin, but it is also produced by skeletal muscle. Exercise boosts muscle BDNF expression and circulating BDNF (Matthews et al., 2009; Pedersen, 2011). In muscle, BDNF activates AMPK and promotes lipid oxidation, linking muscle activity to metabolic adaptation (Pedersen, 2011). While studies have focused on contraction-induced BDNF, it is plausible that stretch similarly increases its expression as part of the exercise-response program. Indeed, BDNF and other neurotrophins often rise with mechanical strain in muscle and contribute to the muscle–brain endocrine loop (Matthews et al., 2009; Pedersen, 2011).

SPARC (Secreted Protein Acidic and Rich in Cysteine). SPARC is a matricellular protein secreted by muscle during exercise. It has roles in metabolism and cancer suppression. Notably, SPARC expression in muscle is sensitive to stretch: Aoi et al. (2012) and others reported that passive muscle stretching or exercise-induced stretch upregulates SPARC secretion from muscle (Aoi et al., 2012). Thus, SPARC is one of the few myokines specifically noted to respond to stretch in addition to contraction (Aoi et al., 2012). Through AMPK and glucose uptake pathways, muscle-derived SPARC appears to mimic some effects of exercise at distant tissues, making it a candidate mediator of stretch-induced metabolic benefits.

Other myokines (e.g., IGF-1, IL-15, FGF-21) are likewise induced by mechanical stimuli, but the above represent key examples. Overall, the evidence suggests that muscle stretching engages the same general network of exercise-responsive genes and secreted factors as active contraction does (Booth et al., 2012; Pedersen, 2011). Integrating across studies, stretch-induced mechanotransduction leads to an increase in anabolic and oxidative myokines (IL-6, irisin, BDNF, SPARC, IGF-1) and a decrease in atrophy/myostatic factors (myostatin) (Yoon et al., 2020; Pedersen, 2011).

Molecular pathways linking stretch to myokine gene regulation

Mechanotransduction in muscle involves known pathways that intersect with myokine transcription. In particular:

• Integrins/FAK⟶MAPK/Akt: As above, integrin activation by stretch recruits FAK and activates MAPKs (ERK1/2, p38, JNK) (Mitra et al., 2005; Chambers et al., 2009). These kinases phosphorylate transcription factors and coactivators (e.g., AP-1, MEF2, CREB) that drive myokine gene expression. For example, p38 has been directly implicated in IL-6 promoter activation during Ca^{2+}-dependent stimuli (Chambers et al., 2009). Akt/mTOR signaling (also downstream of integrin/ILK and growth factors) can modulate translation of myokines or their regulators.

• YAP/TAZ (Hippo pathway): Stretch-induced cytoskeletal tension releases YAP/TAZ to translocate to the nucleus (Fischer et al., 2016). YAP/TAZ then coactivate TEAD transcription factors to promote genes involved in growth and survival. In muscle cells, YAP activation enhances hypertrophy and regeneration, and preliminary evidence suggests it may upregulate some secreted factors (though specific myokine links remain an active research

area). YAP/TAZ thus represent a direct sensor of stretch that likely influences the myokine secretion profile during mechanostimulation (Fischer et al., 2016).

• Calcium signaling: Stretching activates mechano-gated Ca^{2+} entry (e.g., via Piezo1 or TRPC channels). The resulting Ca^{2+} influx can trigger CaMK and calcineurin/NFAT cascades, which influence myokine gene networks. Indeed, IL-6 expression in muscle has been shown to depend on Ca^{2+}-activated pathways as well as p38/JNK (Kanzleiter et al., 2014). Also, increases in intracellular Ca^{2+} may augment mitochondriogenesis and PGC-1α transcription, indirectly boosting PGC-1α–driven myokines like irisin.

• Other mechanosensors: The dystrophin–glycoprotein complex and nuclear LINC complex also convey tension to intracellular pathways. Additionally, mechanical stimuli can activate G protein–coupled receptors and downstream RhoA/ROCK signaling, affecting cytoskeletal dynamics and YAP. As a result, virtually every major growth and stress-response pathway (ERK, p38, NF-κB, Hippo, RhoA, etc.) can be engaged by stretch. The net effect of these signals is to induce an adaptive transcriptional program in the myocyte, part of which is secretion of myokines (Vogel & Sheetz, 2006; Zhang et al., 2022). Figure 1 shows part of the proposed mechanotransduction pathways for myokine release.

Importantly, in vitro models confirm that mechanical stretch alone (without chemical agonists) is sufficient to alter myokine expression. For instance, one study using Flexcell stretch of differentiated myotubes found that even 2% static stretch activated ERK1/2 and p38 phosphorylation and increased secretion of factors like FGF2 and IGF-1 (Koutsilieris et al., 2020). Similarly, cyclic stretch protocols upregulate muscle genes associated with hypertrophy and metabolism through these mechanotransductive routes (Chambers et al., 2009; Koutsilieris et al., 2020).

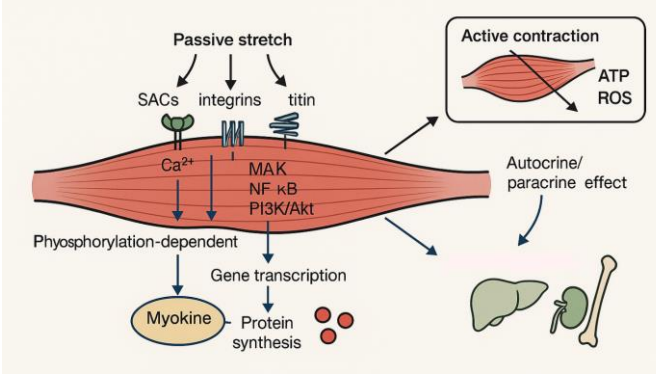

Figure 1. Mechanotransduction pathways for myokine release in stretched skeletal muscle

Implications for therapy and performance

The mechanotransductive release of myokines by stretching has several potential applications.

• Aging and sarcopenia: With age, reduced physical activity leads to sarcopenia and diminished myokine secretion, which in turn exacerbate metabolic decline (Booth et al., 2012). Regular exercise counteracts this by boosting myokines. Notably, passive stretching (e.g., in physiotherapy or passive exercise) may partially substitute for active contraction in populations unable to exercise. By stimulating mechanosensitive pathways, stretching could help maintain myokine signaling in the elderly or immobilized, potentially slowing muscle loss and metabolic deterioration (Booth et al., 2012; Yoon et al., 2020). For example, elevated IL-6 and irisin from stretch might improve glucose metab lism and mitochondrial function in aged muscle.

• Metabolic disease: Myokines mediate many benefits of exercise on obesity and diabetes. IL-6 enhances hepatic glucose production and lipolysis acutely, while irisin promotes adipose browning and energy expenditure. If stretch reliably induces these factors, it could be a low-impact intervention for metabolic syndrome. Indeed, animal models of passive stretch show improved insulin sensitivity and reduced inflammation, plausibly via myokine pathways. Stretching of limbs has also been shown to increase blood flow and nutrient uptake, which might act synergistically with myokine release to improve insulin action.

• Rehabilitation and injury: After injury or surgery, passive range-of-motion exercises are often prescribed. These stretching regimens may help not only by maintaining joint mobility but also by keeping muscle metabolism and endocrine function active. Myokines like IGF-1 and SPARC (release of which is augmented by stretch; (Aoi et al., 2012)) can promote tissue repair and angiogenesis in adjacent tissues (e.g., bone, tendon). For example, the recent study by Eliasson et al. (2025) showed that static loading of myoblasts increased secretion of IGF-1 and other factors that stimulated tendon cell migration (Eliasson et al., 2025). Thus, muscle stretching might aid wound healing through paracrine myokine effects.

• Athletic Performance: Even for healthy athletes, targeted stretching protocols could modulate myokine profiles. Acute stretching sessions might transiently raise beneficial myokines without fatigue. Over time, specific stretch “doses” could potentially prime muscle for growth or endurance (e.g., by reducing myostatin or enhancing PGC-1α-driven myokines). While speculative, understanding how stretch intensity/frequency influences myokines (as begun by Yoon et al., 2020) could allow the design of training regimens that harness these endocrine signals.

Conclusion

In conclusion, skeletal muscle stretching – whether active or passive – is a potent mechanotransductive trigger that can lead to the expression and secretion of key myokines. This process relies on integrin-based adhesions, cytoskeletal tension, and stretch-activated channels to activate YAP/TAZ, MAPKs, Ca^{2+}-dependent kinases, and other signaling pathways (Vogel & Sheetz, 2006; Zhang et al., 2022). The net effect is upregulation of growth- and metabolism-promoting myokines (IL-6, irisin, BDNF, SPARC, etc.) and downregulation of atrophy signals like myostatin (Yoon et al., 2020; Pedersen, 2011). These myokines mediate systemic benefits: improving glucose/fat metabolism, bone health, and neural function. Harnessing this stretch–myokine axis has promising implications for aging populations, metabolic disease therapy, and rehabilitation strategies. Future studies should further delineate the optimal "dose" of stretching to maximize beneficial myokine release and clarify tissue-specific effects of individual myokines in response to mechanotransduction.

What is already known on this subject?

Skeletal muscle functions not only as a force generator but also as an endocrine organ that secretes myokines – signaling cytokines and peptides released by muscle fibers.

What this study adds?

skeletal muscle stretching – whether active or passive – is a potent mechanotransductive trigger that can lead to the expression and secretion of key myokines.

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Data availability

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Compliance with ethical standards

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Author contributions

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