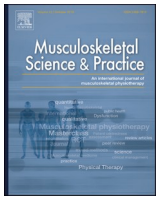
Musculoskeletal Science and Practice 82 (2026) 103507

Contents lists available at ScienceDirect

Musculoskeletal Science and Practice

journal homepage: www.elsevier.com/locate/msksp



Review article

# Neuroimmune interactions in fascia and myofiber regeneration: a narrative review

Robbert N.van Amstel [a,b,*], Ivo J. Lutke Schipholt [c,d], Guido Weide [a,b], Annelies L. Pool-Goudzwaard [b,e], Richard T. Jaspers [a,b]

[a] Laboratory for Myology, Department of Human Movement Sciences, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, the Netherlands
[b] Department of Human Movement Sciences, Faculty of Behavioural and Movement Sciences, Neuromechanics, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, the Netherlands
[c] Department of Clinical Chemistry, Laboratory Medical Immunology, Amsterdam UMC, Location AMC, Amsterdam, the Netherlands
[d] Department of Human Movement Sciences, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences - Program Musculoskeletal Health, the Netherlands
[e] SOMT, University of Physiotherapy, Amersfoort, the Netherlands

ARTICLE INFO

*Keywords:*
Fascia
Muscle
Regeneration
Neuroimmunomodulation
Musculoskeletal manipulations

ABSTRACT

When not treated adequately, neuromusculoskeletal, tendinous, and joint tissue injuries may become chronic, leading to impaired tissue function due to fibrosis, extracellular matrix densification, and fatty connective tissue accumulation, ultimately resulting in reduced joint and muscle mobility. Timely treatment involving the mobilization of fascia and targeted muscle exercise has been shown to enhance and promote tissue regeneration. Key phases in tissue regeneration after injury include the activation of the innate immune system, followed by its resolution. Although several treatment modalities are effective in restoring tissue function, their success rate and time to recovery may still need optimization. Over recent decades, increasing attention has been given to the role of fascia in neuromuscular tissue function, adaptation, and regeneration. However, the complex interactions between fasciae, myofibers, and the immune system remain insufficiently understood, particularly regarding the mechanisms underlying fibrosis, extracellular matrix densification, and chronic pain. Fasciae are interconnected connective tissue sheaths that maintain anatomical organization, allow tissue gliding, and facilitate mechanical force transmission between structures. Because of their mediating role in mechanical and biochemical signalling, fascial tissues are also involved in injury and regeneration processes. Pathological stiffening of fascial connections may impair regeneration by limiting mobility and disrupting mechanotransduction. Therefore, treatment strategies that target both muscle and fascial tissues may offer improved outcomes in the recovery of neuromusculoskeletal function.

## 1. An introduction to fascia anatomy in relation to skeletal muscle and neuroimmune interactions

Skeletal muscles largely consist of fascia and myofibers, providing both active and passive stiffness. Active stiffness is determined by actin-myosin interaction, which results in contractile activity of the myofibers, whereas passive stiffness is influenced by titin and myofascia (Purslow, 2010, 2020, Van Amstel et al., 2025b, Willard et al., 2012). Myofascia is defined as a scaffold for myofibers, consisting of several interconnected structures: the epimysium, perimysium, endomysium, and tendon (Bordoni et al., 2022, Schleip et al., 2019b). In addition, the deep fascia is defined as a strong and dense sheath of connective tissue that extends throughout the entire body and compartmentalizes skeletal muscles and bones (Schleip, Hedley, 2019b). The superficial fascia connects the deep fascia with the (epi)dermis (Fede et al., 2025). All phenotypes of fascia (fasciae) are viscoelastic fibrous connective tissues composed of a ground substance consisting of hyaluronan, glycosaminoglycans, proteoglycans, and glycoproteins, which is reinforced by

This article is part of a special issue entitled: Neuro Immune System published in Musculoskeletal Science and Practice.

* Corresponding author. Vrije Universiteit Amsterdam, Department of Human Movement Sciences, Van der Boechorststraat 7, 1081 BT, Amsterdam, the Netherlands.
*E-mail address:* r.n.van.amstel@vu.nl (R.N.van Amstel).

https://doi.org/10.1016/j.msksp.2026.103507
Received 13 November 2025; Received in revised form 27 January 2026; Accepted 28 January 2026
Available online 5 February 2026

collagen, reticular, and elastin fibers (Van Amstel, Weide, 2025b).

In general, within human fasciae, fibroblasts, myofibroblasts, and fasciacytes are the predominant cells responsible for extracellular matrix production (Chapman et al., 2017, Langevin et al., 2004, Schleip et al., 2019a, Stecco et al., 2018). In the myofascia, muscle stem cells (MuSCs) reside adjacent to muscle fibers, where they contribute to local muscle regeneration (Huijing and Jaspers, 2005; Mauro, 1961, Pirri et al., 2024a). In addition, myoblasts (activated muscle stem cells that proliferate and fuse with uninjured myofibers or form myotubes within injured myofibers), fibro-adipogenic progenitors, and immune cells (e.g., neutrophils, mast cells, and macrophages) have been identified, and they may play regulatory roles in the adaptation and regeneration of myofascia and muscle fibers (De Micheli et al., 2020, Kosmac et al., 2018, Moratal et al., 2018). However, only limited evidence exists for the presence of immune cells in deep fascia, and most reports describe them in pathological conditions (Wang et al., 2025, Zheng et al., 2025).

Within fasciae, specialized sensory cells are present, such as nociceptors, mechanoreceptors, thermal receptors, and polymodal receptors, responding to mechanical, thermal, and chemical stimuli, respectively. Nociceptors also respond to substances and signalling molecules produced by immune cells and release neuropeptides to which immune cells are responsive, indicating biochemical neuroimmune interactions within the fascia (Fede et al., 2022, Stecco et al., 2007). The deep fascia and myofascia exhibit a high density of nerve fibers and various immune cells. These fibres and cells help maintain local homeostasis (Suarez-Rodriguez et al., 2022), particularly in areas with high shear stress and strain (Berrueta et al., 2023). Fascial tensile and shear stresses are thought to transmit mechanical forces and thereby stress and extracellular matrix strain the encapsulated cells via integrins, cadherins, caveolae, glycocalyx core proteins, and stretch-activated ion channels, enabling the cells to sense mechanical loads and initiate mechanotransduction (Huijing and Jaspers, 2005; Ingber, 2006, Pirri et al., 2023a, Xu et al., 2014). Mechanotransduction (Ingber, 2006) is the process by which cells convert mechanical cues into biochemical signals, activating cellular pathways and influencing their function. As immune responses are governed by signals from the microenvironment, physical cues from the fascia, in addition to biochemical signals, may shape immune function and interaction between cells.

Neuroimmune interaction can become dysregulated due to psychological stress, trauma, and hormonal imbalances, all of which are common in conditions such as chronic fatigue, fibromyalgia (Meade and Garvey, 2022), and recurrent/chronic skeletal muscle (micro)injuries (Yang and Hu, 2018). When neuroimmune interactions become dysregulated, they can lead to both local tissue effects and consequences within the nervous system (central and peripheral) (Ji et al., 2018). Hypothetically, changes in local tissue stiffness may modify force vector transmission and stiffness-dependent biochemical signalling, redistributing mechanical load and altering afferent input via mechanosensitive sensory cells, including nociceptors and proprioceptors. Despite existing findings, there is still a lack of understanding about how local inflammation interacts with neuroimmune processes and how mechanotransduction, induced by manual interventions, influences fascia and myofiber regeneration after muscle and fascia (micro)injury. Prolonged local inflammation may hinder fascia regeneration, while inadequate recovery could lead to dysregulated neuroimmune interactions and tissue impairments. This narrative provides an overview of these mechanisms by evaluating the effects of manual interventions in animal and *in vitro* studies (studies of cellular effects outside the body), and to identify in current research gaps.

## 2. Fascia and myofiber regeneration

When (micro)injury occurs in the fascia and myofibers, this clearly triggers a complex recovery process involving multiple cells and biochemical signalling pathways (Table 1) (Bentzinger et al., 2012). This process **consistently** consists of three main phases: bleeding and inflammation (day 0–5), proliferation (day 5–21), and remodelling (day 21>) (Bentzinger et al., 2013). Successful regeneration **generally** requires a tightly regulated sequence of these phases, primarily regulated by the local microenvironment and immune cells such as neutrophils and macrophages (Bentzinger et al., 2013). During the early inflammatory phase, neutrophils are recruited to the site of injury, followed by monocytes that differentiate into proinflammatory macrophages. These macrophages critically play a crucial role in clearing damaged tissue and initiating the repair and remodelling of the tissue. This initial

**Table 1**
**Molecular Mediators of Inflammation.**
This table provides an overview of the mechanisms of action of the molecules discussed in this paper, summarizing their roles in pro- and anti-inflammatory processes.

| Biochemical Molecules | Effects | Inflammatory | |
|---|---|---|---|
| | | Pro | Anti |
| **TGF-β** | Regulates immune response, fibrosis, and tissue repair. | | ✓ |
| **CTGF** | Promotes tissue fibrosis and extracellular matrix production. | ✓ | |
| **IGF-1** | Promotes muscle growth and regeneration. | | ✓ |
| **MGF** | Involved in muscle repair and growth, similar to IGF-1. | | ✓ |
| **MSTN** | Inhibits muscle growth. | ✓ | |
| **DAMPs** | Activate immune response via pattern recognition receptors. | ✓ | |
| **IL-10** | Anti-inflammatory cytokine that suppresses pro-inflammatory signals. | | ✓ |
| **IL-4** | Promotes differentiation of Th2 cells, contributing to immune regulation. | | ✓ |
| **IL-6** | Pro-inflammatory cytokine, but can have anti-inflammatory effects in muscle repair. | ✓ | ✓ |
| **TNF** | Pro-inflammatory cytokine is involved in systemic inflammation. | ✓ | |
| **PGs** | Mediate inflammation, pain, and fever (depending on subtype, can be pro- or anti-inflammatory). | ✓ (PGE2) | ✓ (PGD2) |
| **5-HT** | Neurotransmitter involved in mood regulation and pain modulation. | ✓ | |
| **BK** | Causes vasodilation and increases permeability, involved in pain response. | ✓ | |
| **HIS** | Mediator of allergic reactions increases vascular permeability. | ✓ | |
| **$H^+$** | Lower pH contributes to pain and acidosis in inflamed tissue. | ✓ | |
| **SP** | Neurotransmitters involved in pain perception and inflammation. | ✓ | |
| **CRP** | Marker of systemic inflammation increases in response to pro-inflammatory signals. | ✓ | |
| **CTX-1** | Marker of bone resorption, involved in bone turnover | ✓ | |
| **NOS2** | Inducible nitric oxide synthase produces nitric oxide during inflammation. | ✓ | |
| **RANTES** | Chemokine involved in recruiting immune cells to sites of inflammation. | ✓ | |
| **NPY** | Modulates pain and inflammatory responses. | | ✓ |
| **Leptin** | Regulates energy balance, immune response, and may contribute to inflammation. | ✓ | ✓ |

Abbreviations: TGF-β, Transforming Growth Factor Beta; IL-10, Interleukin 10; CTGF, Connective Tissue Growth Factor; DAMPs, Damage-Associated Molecular Patterns; IL-4, Interleukin 4; TNF, Tumor Necrosis Factor; IGF-1, Insulin-like Growth Factor 1; MGF, Mechano-Growth Factor; MSTN, Myostatin; PGs, Prostaglandins; 5-HT, Serotonin (5-Hydroxytryptamine); BK, Bradykinin; HIS, Histamine; $H^+$, Hydrogen ions; SP, Substance P; CRP, C-Reactive Protein; CTX-1, C-Terminal Telopeptide of Type 1 Collagen; NOS2, Nitric Oxide Synthase 2 (Inducible NOS); RANTES, Regulated on Activation, Normal T Cell Expressed and Secreted; NPY, Neuropeptide Y; IL-6, Interleukin 6.

inflammatory phase is followed by a transition towards tissue remodelling, mediated by immune and muscle cell signalling (Wynn and Vannella, 2016).

Inflammation (the first main phase) is widely recognized as a critical component of tissue repair and is initiated when immune cells like neutrophils, macrophages, mast cells, and natural killer cells detect Damage-Associated Molecular Patterns (DAMPs) released by injured tissue (Tu and Li, 2023). These immune cells respond by triggering an inflammatory cascade aimed at eliminating the cause of the injury (Tu and Li, 2023). Monocytes are recruited from the bloodstream and differentiate into proinflammatory macrophages (M1), which, along with neutrophils, effectively help clear cellular debris and eliminate the cause of inflammation (Italiani and Boraschi, 2014). Macrophages become more pro-inflammatory when subjected to mechanical loads (Shan et al., 2019). In addition, mechanical loading of MuSCs and fibroblasts apparently increases the production of insulin-like growth factor-1 (IGF-1) and mechano-growth factor (MGF) (Huijing and Jaspers, 2005). These growth factors not only promote myofiber regeneration, but also likely support the transition of macrophages from a proinflammatory to an anti-inflammatory phenotype (Dort et al., 2019). Moreover, pro-inflammatory macrophages produce cytokines and growth factors such as interleukin-6 (IL-6) and IGF-1, which subsequently promote the proliferation of MuSCs and (myo)fibroblasts (Dort et al., 2019). As the inflammatory response progresses, cells including muscle cells, neutrophils, and macrophages release transforming growth factor-beta (TGF-β), interleukin-4 (IL-4), and interleukin-10 (IL-10), which clearly drive the transition from inflammation to tissue remodelling and connective tissue formation (Wynn and Vannella, 2016) (see Fig. 1).

While the inflammatory process unfolds, hypoxia at the injury site apparently amplifies the response by delaying neutrophil apoptosis, contributing to low oxygen availability, and thereby recruiting additional neutrophils (Talla et al., 2019). The nervous system also potentially plays a regulatory role, modulating inflammation via the inflammatory reflex, in which neural circuits are activated by cytokines and other signals to help resolve inflammation (Pereira and Leite, 2016). As recovery advances, pro-inflammatory mediators are gradually replaced by anti-inflammatory mediators, like TGF-β and IL-10, which clearly promote the resolution of inflammation and the transition to the proliferation phase (the second main phase) of tissue healing (Barnig et al., 2022, Greenlee-Wacker, 2016). The apoptosis of neutrophils and their subsequent clearance by macrophages through efferocytosis are well-established processes in this resolution (Greenlee-Wacker, 2016). Macrophages undergo a phenotypic switch from pro-inflammatory to anti-inflammatory phenotypes (M2), a switch partially mediated by IGF-1, TGF-β, IL-4, and Tumor Necrosis Factor (TNF) (Italiani and Boraschi, 2014). During tissue regeneration, myofibers and fascia undergo adaptation to maintain structural integrity. TGF-β and Connective Tissue Growth Factor (CTGF) **critically** play vital roles in regulating extracellular matrix reorganization and collagen production. Fibroblasts and myofibroblasts are contributors to wound closure, facilitating matrix deposition and contraction of the injury site (Hinz et al., 2019). Additionally, fibro-adipogenic progenitors (FAPs) are involved in the repair response, contributing to both fat deposition and fibrosis (scar tissue) in response to muscle and fascia injury (Fig. 2) (Moratal et al., 2018).

It has been speculated that myofascial force transmission plays a crucial role in skeletal muscle recovery and regeneration (Huijing and Jaspers, 2005). This process involves the transfer of force from fascia to adjacent tissue (Huijing, 2009), resulting in mechanical stress at the basal lamina and encapsulated cells (Huijing, 2009). In response to this mechanical stress, fascia likely adapt their biomechanical properties (e.g., stiffness, elasticity, plasticity, viscoelasticity, and anisotropy). In addition, the mechanical stress applied to transmembrane mechanoreceptors and channels in myofibers and fascia cells apparently modulates protein turnover (gene expression), enhances the secretion of growth factors like IGF-1, MGF, vascular endothelial growth factor (VEGF), and reduces myostatin levels, thereby promoting regeneration (Fig. 2) (Juffer et al., 2014).

These growth factors, alongside anti-inflammatory mediators, clearly promote regeneration in an autocrine (self-signalling) and paracrine (neighbour-signalling) manner. Hence, early joint movement and mechanical loading of injured myofibers and fasciae are presumably essential for optimal recovery.

### 2.1. *Discussion and future directions*

Although inflammatory and regenerative pathways are well characterized, their functional implications remain equivocal. Mechanical loading and growth factor signalling (e.g., IGF-1, TGF-β) appear essential for regeneration but are also associated with fibrosis and maladaptive remodelling. These inconsistencies likely depend on load magnitude, timing, and cellular context. Future human studies integrating mechanobiology, immune phenotyping, and longitudinal imaging are required to distinguish regenerative from pathological myofascial adaptations.

## 3. Chronic fascia injury causes prolonged inflammation, which can alter skeletal muscle quality

Failure to resolve inflammation or repeated stimulation of the immune response can **clearly** lead to prolonged tissue inflammation (Generaal et al., 2014). Collagen is the primary component of fascia, predominantly types I and III, which consistently form a structural framework for myofibers (Fede et al., 2021b). Collagen type I is stiffer than type III, and prolonged inflammation may significantly alter the extracellular matrix, shifting the collagen I/III balance and promoting

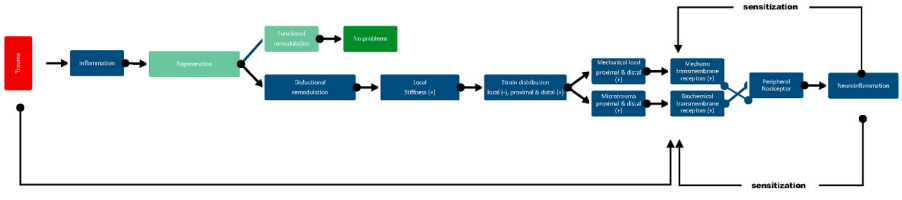



**Fig. 1. Trauma initiates nociceptive and inflammatory responses via DAMPs, interleukins, cytokines, and prostaglandins (see Figs. 2 and 3).** After the inflammatory phase (day 0–6), the regeneration phase begins (day 7–21), followed by tissue remodelling (> day 21). Optimal recovery results in functional tissue remodelling during the healing process. However, incomplete regeneration alters tissue composition (↑ collagen I, ↓ collagen III and hyaluronan) and leads to dysfunctional remodelling, increasing local stiffness. Due to this increased stiffness, mechanical strain is redistributed to adjacent tissues, activating transmembrane mechanosensitive channels (e.g., Piezo and TRP channels) on nociceptor cells, thereby triggering pain sensation. When strain exceeds the strain breakpoint, local microtrauma may occur proximal or distal to the stiffened region. Repetitive overstress to these surrounding tissues activates peripheral nociceptors, leading to neuroinflammation and ultimately to sensitization, making their transmembrane channels increasingly sensitive.

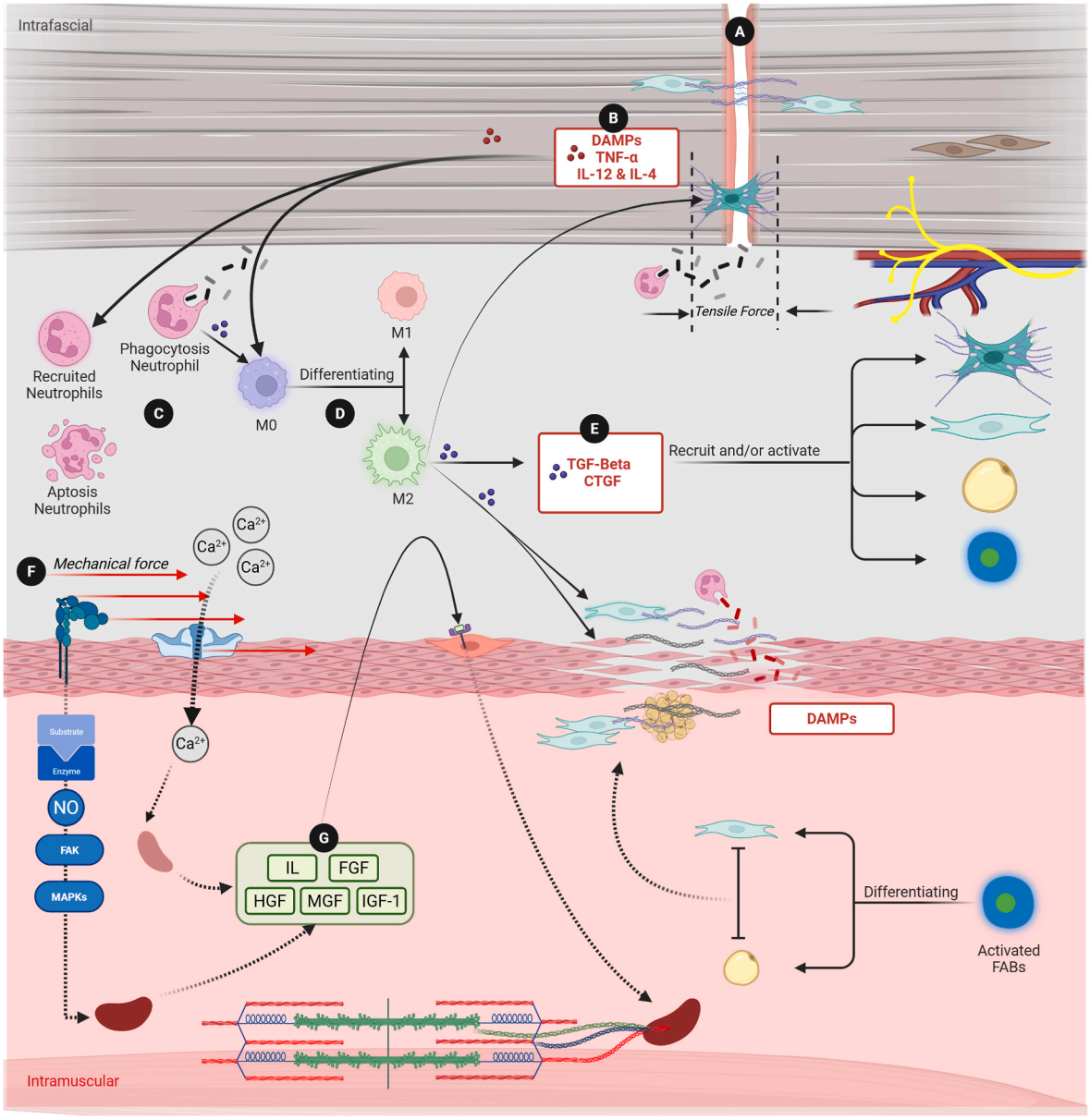



**Fig. 2. Schematic representation of skeletal muscle (myofascial and myofiber) regeneration.**
This schema provides a simple representation of skeletal muscle recovery and regeneration after (micro)injury. **A–D, M1)** This represents the bleeding and inflammation phase (day 0 to day 5), where D marks the differentiation from M0 to M1. **D–G, M2)** corresponds to the proliferation and modulation phase (approximately day 5 to day 21), where D marks the differentiation and/or polarization into M2. The figure also represents myofascial shear forces (F) induced by training. **A)** In response to excessive stress, such as overstretching, overuse, or (micro)injury of tissues, **B)** danger-associated molecular patterns (DAMPs), Tumor Necrosis Factor-α (TNF-α), and interleukins can be released. These matrix components C) recruit neutrophils, which clear the damaged tissue and release Transforming Growth Factor Beta (TGF-β) to initiate tissue repair. **D)** Locally, biochemical molecules drive the differentiation of macrophages-0 (M0) into macrophages-1 (M1) or macrophages-2 (M2). **E)** M2 macrophages produce large amounts of TGF-β, which recruits and activates adipocytes, myoblasts, fibroblasts, myofibroblasts, and fibro-adipogenic progenitors, promoting muscle recovery. **F)** Mechanical forces cause tensile and shear stress applied to transmembrane mechanoreceptors and channels of myofibers and fascia cells, **G)** enhancing the secretion of growth factors such as Insulin-like Growth Factor-1 (IGF-1) and Mechano-Growth Factor (MGF), and reducing myostatin levels, thereby modulating protein turnover (gene expression); thereby promoting muscle recovery and regeneration.

hyaluronan aggregation, resulting in densification and increased stiffness of the fascial matrix (Pratt, 2021, Stecco et al., 2023, Stecco et al., 2022).

Lumbar fascia injury in mice robustly triggers macrophage infiltration, with fascia containing significantly more macrophages than adjacent fat tissue (6.8% ± 0.79% vs 2.0% ± 0.48%; $P < 0.01$), indicating a local immune response (Bi et al., 2023). In addition, exposure to physical tasks after injury apparently upregulates collagen type I and CTGF, while high-force tasks clearly increase CTGF, TGF-β, and collagen I expression (Abdelmagid et al., 2012). In addition, rats subjected to high-force tasks for up to 18 weeks consistently exhibited elevated levels of TNF-α and fibrogenic proteins (Fisher et al., 2015, Hilliard et al., 2021). While inflammation subsided by week 18, persistent fibrosis was observed, relating to declines in sensorimotor function (Fisher et al., 2015). This strongly suggests that prolonged elevated levels of fibrogenic proteins may contribute to excessive fibrosis development within and surrounding the fascia, as seen in mice (Bishop et al., 2016, Jiang et al., 2020, Kirchgesner et al., 2019, Lee et al., 2024). Similarly, rat models with induced peripheral nerve injury demonstrated a significant decrease in hyaluronan concentration and an increase in collagen

deposition in both the skeletal muscles and thoracolumbar fascia, particularly on the injured side (Zhao et al., 2024). These findings were similarly mirrored in porcine models following thoracolumbar fascia injury and 8 weeks of leg mobility restriction, where thickening of the thoracolumbar fascia was observed (Bishop et al., 2016). A thickening of the thoracolumbar fascia is commonly observed in patients with chronic low back pain, with mean fascia thickness of 2.11 ± 0.65 mm in patients versus 1.75 ± 0.85 mm in healthy controls ($p < 0.05$) (Pirri et al., 2023b), and a ~25% increase in perimuscular connective tissue thickness, including thoracolumbar fascia and epimuscular fat, compared with healthy controls ($p < 0.01$) (Langevin et al., 2009). However, imaging outcomes, including ultrasound assessments of thoracolumbar fascia thickness, are influenced by spatial and temporal resolution. In 2D ultrasound, speckle patterns can limit the precision of thickness measurements (Pirri et al., 2024b), and if speckle tracking is used for dynamic analysis, measurement variability may increase (Van Amstel et al., 2025a). Low temporal resolution further reduces accuracy in capturing rapid tissue changes, which may partly explain variability in reported fascia thickness across studies. 3D ultrasound imaging with state-of-the-art devices and high spatial resolution (small voxels) may reduce partial volume effects and improve the accuracy of lumbar muscle and epimuscular connective tissue measurements, showing clear potential, although further validation and research are still required (Rummens et al., 2024, Weide et al., 2017). Nevertheless, these findings cautiously suggest that prolonged immune response and fibrogenic activity may contribute to fascia thickening and functional decline associated with chronic low back pain, although direct evidence in humans remains limited.

In patients with chronic systemic inflammation and pain, elevated levels of inflammatory mediators, like various cytokines, chemokines, and growth factors, strongly suggest the presence of chronic low-grade inflammation (Bäckryd et al., 2017, Hysing et al., 2019). The prolonged presence of pro-inflammatory immune cells, such as macrophages (Morris et al., 2020, Sanabria-Mazo et al., 2022), likely drives the chronic overexpression of TGF-β1 and CTGF (Zimowska et al., 2017). These inflammatory mediators clearly promote fibrosis by increasing local collagen production by fibroblasts (Pan et al., 2020, Zhang et al., 2024), myofibroblasts, and MuSCs (Hillege et al., 2022, Shi et al., 2021). Additionally, prolonged tissue inflammation may attract adipocytes to the affected area (Côté et al., 2017), exacerbating fibrosis and fat accumulation both within and outside the fascia (Hodges and Danneels, 2019, Kondrup et al., 2022), altering its biomechanical properties (Brandl et al., 2024, Koppenhaver et al., 2020, Langevin et al., 2011). Altered fascial biomechanical properties are expected to reduce the local shear stress and strain between the deep fascia, myofascia, and myofibers (Maas, 2019), which is presumably expected to disrupt the mechanotransduction to their encapsulated cells (Van Amstel, Weide, 2025b). The disruption of mechanotransduction likely hinders the release of growth factors and anti-inflammatory mediators, both critically important for dampening inflammation and essential for skeletal muscle regeneration (Du et al., 2023). Failure of skeletal muscle regeneration due to prolonged tissue inflammation may lead to fascia and myofiber denervation (loss of nerve supply), initiating a cascade of tissue inflammation and further apparently causing fat and fibrosis accumulation (Hodges et al., 2021, Pavan et al., 2014). This loss of nerve supply, combined with the overproduction of collagen by fibroblasts in response to persistent inflammation, clearly degrades the quality of both fascia and myofiber, making these tissues more susceptible to recurrent (micro)injuries (Bogdanov et al., 2021, Hodges and Danneels, 2019).

In conclusion, a prolonged pro-inflammatory environment substantially impairs fascia and muscle regeneration by attracting adipocytes and activating fibroblasts, leading to excessive local collagen deposition, shifting the balance between collagen types I and III, fat accumulation, and fibrosis within and around the fascia and muscle. This process ultimately increases local stiffness, which negatively affects the fascial viscoelastic properties. These altered viscoelastic properties consequently reduce local strain at the stiffened region, thereby increasing vulnerability to strain injury in the areas adjacent to the stiffened region. In addition, increased stiffness in the connections between fascia and myofibers likely restricts their relative movement, thereby disrupting shear strain and hindering the cellular processes **critically** essential for repair and regeneration (Huijing and Jaspers, 2005).

### 3.1. *Discussion and future directions*

Although animal and clinical studies consistently link prolonged inflammation to fascial thickening and fibrosis, its causal relationship with altered biomechanics, such as increased stiffness, in humans remains equivocal. Load intensity, duration, and neural integrity are critical modifiers, yet thresholds for adaptive versus maladaptive remodelling remain unclear. Future studies should integrate human in vivo imaging, immune profiling, and biomechanical assessments to elucidate interactions between chronic inflammation, altered mechanotransduction, and musculoskeletal disorders like low back pain.

## 4. Local neuroimmune interactions affect neuronal excitability

Fasciae are **densely** innervated tissues in the musculoskeletal system (Fede et al., 2021a, Suarez-Rodriguez et al., 2022). Increased fascial stiffness may alert immune cells to the possibility of tissue injury. In addition, changes in mechanical cues through mechanotransduction can potentially alter the local biochemical milieu, thereby triggering a local immune response and possibly modifying neuronal excitability during neuroimmune interactions (Du et al., 2023; Van Amstel, Weide, 2025b). In this context, local stiffened extracellular matrix or crosslinks within and/or between anatomical structures can apparently change the direction of force vectors generated by myofibroblast contraction, muscle contraction, and/or passive joint motion. This redirected tension can act on neighboring cells, effectively activating their mechanosensitive channels in sensory cells, potentially increasing their activity and further influencing neuronal excitability. It is possible that increased local stiffness keeps embedded sensory cells like nociceptors silent, while surrounding nociceptors become overloaded and more easily excitable, moving closer to their stress threshold.

From skin to bone, structures like the superficial fascia, deep fascia, myofascia, myofibers, and arthrofascia are clearly innervated by nerve fibers from the neurovascular tract (Van Amstel, Weide, 2025b). These nerve fibers contain both myelinated and unmyelinated efferent and afferent fibers, with conduction velocities in the range of Aα fibers (motor), Aβ fibers (mechanical conduction), C fibers, and Aδ fibers (nociceptive conduction) (Fede, Petrelli, 2021a, 2022; Mense, 2019). Anatomical studies in human cadavers and animals have consistently shown a high density of various mechanosensitive sensory cells within the fasciae, including Meissner's bodies, Pacini bodies, Ruffini endings, and Golgi-Mazzoni corpuscles, and nociceptors (Fede et al., 2022; McLain and Pickar, 1998; Mense, 2019; Stecco et al., 2007, Tomlinson et al., 2020, Yahia et al., 1992).

In pain-free adults, hypertonic saline injections into the lumbar deep fascia resulted in greater pain intensity and duration than injections into the superficial fascia or erector spinae muscle (Schilder et al., 2014, Vogel et al., 2022). The pain was described as burning, throbbing, and stinging, clearly indicating Aδ and C-fiber nociceptor involvement (Schilder et al., 2014). Another study confirmed that injections into the lumbar deep fascia led to higher pain levels and larger pain areas compared to injections into back muscles. In addition, larger fluid volumes consistently resulted in significantly more intense and widespread pain than smaller volumes (Vogel et al., 2022). These findings strongly highlight the dense innervation of the deep fascia and emphasize its role in afferent signalling.

Sensory cell receptors can be activated biochemically by sensitizing substances (e.g., inflammatory mediators) and mechanically via

mechanosensitive channels (e.g., piezo-gates and transient receptor potential channels) (Heppenstall and Lewin, 2006; Yang and Plotnikov, 2021). Biochemical channels are specifically sensitive to inflammatory mediators, such as prostaglandins, serotonin, bradykinin, histamine, $H^+$ ions, and Substance-P. Mechanosensitive channels include pro-nociceptive types, such as Piezo1-channels, transient receptor potential channels, and nociceptive types, such as two-pore domain potassium channels (Della Pietra et al., 2024). These channels effectively modulate nociceptive excitability at low thresholds (Heppenstall and Lewin, 2006) and regulate the passage of $Na^+$, $Ca^{2+}$, and $K^+$ ions through the plasma membrane, thereby triggering the nociceptor excitability (Della Pietra, Gómez Dabó, 2024). Activation of these channels clearly plays a key role in regulating nociceptor excitability, contributing to the onset and persistence of nociception through both biochemical and mechanical pathways.

In chronic constriction injury rat models, in which the sciatic nerve is loosely ligated with chromic gut sutures to induce mild chronic compression, immune cells, including T lymphocytes (Moalem et al., 2004) and neutrophils (Morin et al., 2007), actively migrate to the dorsal root ganglia and contribute to neuro-immune signalling. In mouse models, TGF-β was found to significantly influence macrophages and microglia in the dorsal root ganglia, thereby contributing to an inflammatory response associated with neuropathic pain (Yu et al., 2020). Sensory neuron-associated macrophages also enhance nociceptive neuron hyperexcitability by releasing TNF-α and interleukins, which attract other immune cells (Santa-Cecília et al., 2019). Furthermore, in rat models, increased reactive oxygen species production following spinal nerve ligation (tight ligation) substantially contributed to the development of neuropathic pain (Kim et al., 2004).

Myofibroblast contraction may also activate mechanosensitive channels in sensory cells, potentially increasing their activity and leading to a change in neuronal excitability (Schleip, Gabbiani, 2019a; Schleip and Klingler, 2019). In-vitro research has revealed that TGF-β stimulates myofibroblast and fibroblast contractions, which mechanically apply tension to the extracellular matrix of the fascia via integrins (Schleip, Gabbiani, 2019a; Schleip and Klingler, 2019). These contractions likely stiffen the fibrous tissues and effectively activate mechanosensitive channels in nearby nociceptors within the fascia (Castella et al., 2010, Tomasek et al., 2002).

In conclusion, fasciae are densely innervated anatomical structures, and nociceptor excitability can be substantially influenced by both biochemical and mechanical stimuli. Inflammatory mediators from macrophages and neutrophils clearly contribute to hyperexcitability, while myofibroblast contraction, together with stiffened extracellular matrix or crosslinks between anatomical structures, can apparently redirect mechanical forces toward neighboring cells, thereby activating their mechanosensitive channels and further enhancing neuronal excitability.

### 4.1. Discussion and future directions

Fasciae are densely innervated, and nociceptor excitability is influenced by both biochemical mediators and mechanical forces. While myofibroblast contraction, matrix stiffening, and inflammatory signalling clearly affect neuronal activity, the precise thresholds for pathological versus adaptive responses remain unclear. Future studies should combine human neuroimaging, mechanosensitive channel profiling, and biomechanical mapping to clarify how fascial stiffness, neuroimmune interactions, and mechanotransduction contribute to pain onset and chronicity.

## 5. Peripheral neuroimmune interactions and spinal neuroinflammation

There is a growing interest in understanding sterile neuroimmune interactions within the spinal cord and supraspinal regions, collectively known as neuroinflammation. Peripheral and central neuroimmune interactions are closely interconnected, with various tissues, including nerves, bones, fasciae, and skeletal muscles, capable of triggering neuroinflammatory responses (Sun et al., 2022). A key mechanism linking peripheral and central neuroimmune interactions is neurogenic neuroinflammation, where C-fiber peptidergic nociceptor activation directly leads to the release of neuropeptides within the spinal cord (Xanthos and Sandkühler, 2014). These neuropeptides may induce neuroimmune interactions both in peripheral tissues (neurogenic inflammation) and within synapses between first- and second-order neurons, resulting in neurogenic neuroinflammation in the central nervous system (Xanthos and Sandkühler, 2014).

Tissue-derived inflammatory mediators act locally through autocrine and paracrine signalling, but can also contribute to systemic inflammation (Perry, 2004). Systemic inflammatory mediators potentially can enter the brain through leaky regions near the brain, such as the choroid plexus and circumventricular organs, thereby initiating neuroinflammatory responses. Furthermore, immune cells primed in injured tissues may migrate into the central nervous system through these leaky regions, guided by high concentrations of chemokines (D'Mello et al. , 2009).

Much of this understanding comes primarily from animal studies, and the direct applicability to humans remains uncertain. Nevertheless, preliminary evidence strongly suggests that neuroinflammation is present in humans with musculoskeletal conditions (Sandström et al., 2022, Torrado-Carvajal et al., 2021). However, the specific triggers and determinants of neuroinflammation and how these relate to (chronic) pain are still largely unclear (Ji et al., 2018). For instance, in rats injected in the paw with complete Freund's adjuvant (an immune activator), only one of six animals showed increased microglial activation, indicating minimal spinal neuroinflammation (Miller et al., 2013). In contrast, rats with osteoarthritic pain showed an approximately 25% ipsilateral increase in microglial marker binding compared with contralateral tissue ($p < 0.05$), and those with nerve injury exhibited a $\geq$70% increase ($p < 0.01$), indicating graded spinal neuroinflammatory responses across models (Miller et al., 2013).

Chronic and/or recurrent (micro)injury of the fascia may potentially lead to neuroinflammation, which could be triggered by prolonged peripheral sensitization. This sensitization might activate neuroimmune and nerve cells in the nervous system, initiating a neuroimmune response that potentially leads to neuroinflammation (Fig. 3). Neuroinflammation can alter the excitability of nociceptive processing, and emerging evidence suggests that supraspinal neuroinflammation may affect not only the sensory aspects of pain but also the cognitive and emotional dimensions. This likely may partially explain the widespread symptoms often seen in patients with musculoskeletal conditions.

### 5.1. Discussion and future directions

While preclinical and emerging human studies highlight the potential role of peripheral fascia injury in driving neuroinflammation and chronic pain, the causal mechanisms, triggers, and thresholds remain largely unknown. Future research should focus on establishing these links in humans and determining how peripheral microinjury contributes to central sensitization and multidimensional pain. Clarifying these mechanisms could ultimately inform targeted therapeutic strategies and improve outcomes for patients with musculoskeletal conditions.

## 6. Neuroimmune interactions, fascia regeneration, and mechanotransduction by manual interventions

Tensile and shear loads applied to skeletal muscle and surrounding fascia have been shown to cause shear and tensile strains within fascia, which subsequently are transmitted to the myofibers, including their MuSCs and myoblasts within their niches on top of the myofibers (Haroon et al., 2021). It is conceivable that macrophages in the

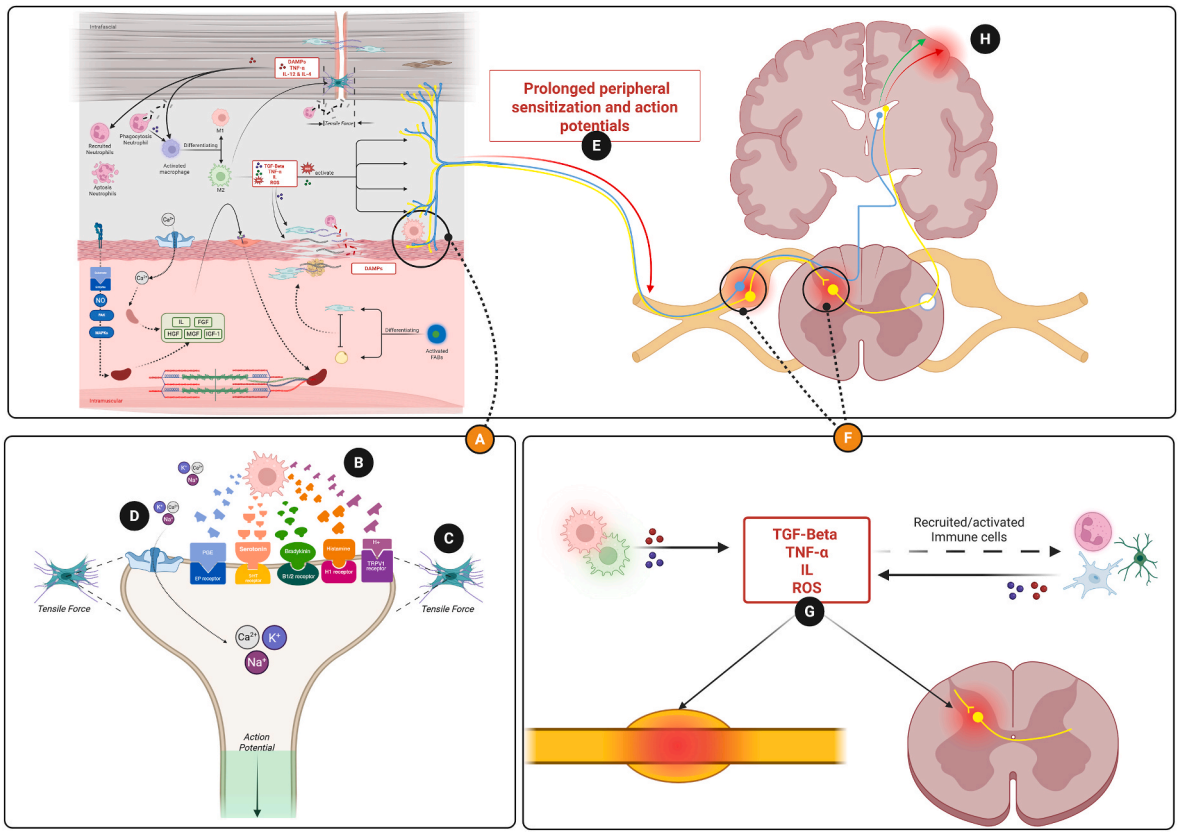



**Fig. 3. Schematic representation of neuroinflammation.**
This schema represents how neuroinflammation can be triggered by prolonged peripheral sensitization. **A)** Sensory cell receptors can be activated **B)** biochemically by sensitizing substances (e.g., inflammatory mediators) released by immune cells and **C)** mechanically by opening mechanosensitive channels (e.g., piezo-gates and transient receptor potential channels) by nearby myofibroblasts. Biochemical channels are sensitive to inflammatory mediators such as prostaglandins, serotonin, bradykinin, histamine, $H^+$ ions, and Substance-P. Mechanosensitive channels include pro-nociceptive types, such as Piezo1 channels and transient receptor potential channels, as well as nociceptive types, such as two-pore domain potassium channels. Both channel types modulate nociceptive excitability at low thresholds. **D)** These channels regulate the passage of $Na^+$, $Ca^{2+}$, and $K^+$ ions in and out of the cell, triggering nociceptor excitability and the generation of action potentials. **E)** Prolonged peripheral sensitization causes continuous action potentials, which can trigger **F)** a neuroimmune response by activating neuroimmune cells (e.g., microglia, astrocytes, oligodendrocytes, and macrophages) and nerve cells in the nervous system, **G)** potentially leading to neuroinflammation. **H)** Neuroinflammation can alter the excitability of nociceptive processing and may affect not only the sensory aspects of pain but also the cognitive and emotional dimensions.

interstitial space between muscle fibers are similarly mechanically loaded as MuSCs in their niche (van Santen et al., 2022). The mechanical loading of both muscle cells and macrophages consistently triggers immunomodulatory responses (Su and Yin, 2025). However, in case of stiffening of the connective tissue and the connection between fascia and myofibers the shearing will be limited or minimized (Fig. 4). It is hypothesized that manual interventions follow the skin displacement principles, which implies that forces applied to the skin are transmitted to deeper structures, including fasciae and muscles, and bones (Van Amstel, Weide, 2025b). These transmitted forces may strain the anatomical structures under the skin beyond their yield point, potentially causing plastic deformation and even breaking collagen crosslinks, both of which likely enhance shear strain between the fascia and underlying myofibers, thereby eliciting immunomodulatory responses (Fig. 4).

There is increasing evidence from animal studies that manual interventions (such as joint and fascia mobilizations) may influence fascia regeneration after injury (Barbe et al., 2022, Barbe et al., 2021b, Bove et al., 2019, França et al., 2020, Loghmani et al., 2021). This introduces new ideas regarding treatment, suggesting that mechanotransduction potentially has important features necessary for normal fascia and myofiber regeneration. This process is thought to activate immune cells, MuSCs, myoblasts, as well as stimulate their differentiation into myotubes and myofibroblasts, simultaneously influencing both immune modulation and tissue regeneration (Van Amstel, Weide, 2025b). In this section, we will discuss the outcome of several in vivo studies on rodent bone, neuronal tissue, and muscle as well as *in vitro* studies, which together provide evidence supporting how mechanotransduction from manual interventions **may** affect neuroimmune interactions and fascia and myofiber regeneration.

In a rat study investigating bone remodelling in response to mechanical loading, rats were randomly assigned to either a control group or a muscle force task group (task group). The rats in the task group performed a high-repetition, high-force lever-pulling task (4 pulls per second at ≥60% of their maximum voluntary force), for 2 h per day, 3 days a week, over 12 weeks. They were subsequently allocated to receive either manual interventions or not (untreated) during the 12 weeks. The manual intervention consisted of forelimb long-axis stretching, wrist flexion/extension joint mobilizations, and forearm massage, applied for approximately 5 min per forelimb, 3 times per week, immediately after each task session. Additionally, some rats in the task groups rested after 12 weeks, either with or without manual interventions. The manual interventions were performed three times per week for approximately 10–14 min in total per rat and resulted in increased osteoblast indices (osteoblasts per bone surface: 6.06 ± SD.49 vs 4.87 ± SD.32, $p < 0.05$; osteoid volume per bone volume: 1.63 ± SD.18% vs 1.23 ± 0.12%,$p < 0.05$), such as alkaline phosphatase, while decreasing osteoclast activity (osteoclast number per bone surface: 1.18 ± SD.14 vs 1.49 ± SD.15; osteoclast surface per bone surface: 3.71 ± 0.35 % vs 4.83 ± 0.29 %, $p < 0.05$) in trabecular bones (Barbe et al.,

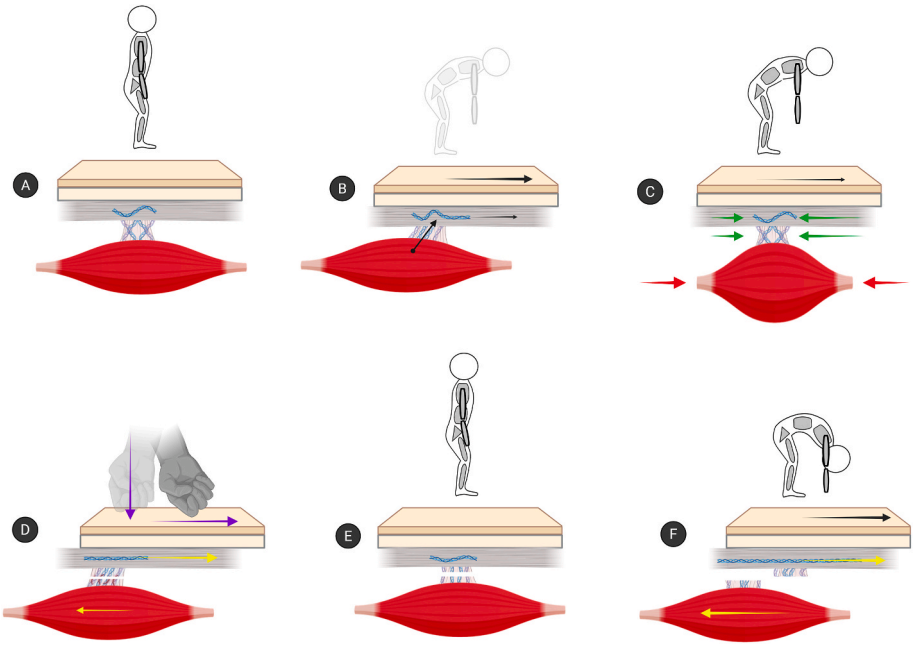



**Fig. 4. Hypothesized mechanism underlying manual interventions based on skin displacement principles**. This schematic illustrates how manual interventions may biomechanically modulate the interaction between fasciae and underlying muscles, which could be crucial for optimizing tissue regeneration. **A)** Upright standing position with intact collagen cross-links between the skin, fasciae, and underlying muscle tissue. **B)** During trunk flexion, longitudinal displacement of the skin, superficial fascia, and deep fascia (black arrows) transmits forces to deeper structures, increasing strain within fascial cross-links and myofibres (black arrow with dot). **C)** Increased strain transmission may elicit a protective muscular contraction to limit excessive deep fascial and myofascial strain. **D)** Manual intervention applies externally induced normal and shear forces to the skin (purple arrow), which are transmitted to deeper tissues (yellow arrows) and may exceed the connective tissue yield point. **E)** Exceeding the yield point may result in plastic deformation and partial disruption of collagen cross-links, altering myofascial force transmission. **F)** During subsequent trunk movements, normalization of deep myofascial shear strain (yellow arrows) is proposed to facilitate effective mechanotransduction and associated immunomodulatory responses. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2022). In contrast, untreated rats showed increased catabolic indices, including decreased trabecular bone volume (approximately 11 % loss relative to controls, $p < 0.01$), increased osteoclast numbers and surface (both significantly higher than controls, $p < 0.05$), mid-diaphyseal cortical bone thinning and altered geometry ($p < 0.05$), and elevated serum levels of C-Terminal Telopeptide of collagen type I (CTX-1) and TNF-α consistent with increased bone resorption and inflammation (Barbe et al., 2022). These findings indicate that manual interventions enhance bone remodelling. These interventions also resulted in increased IL-10 levels (142 ± 15 pg per milliliter vs. 98 ± 12 pg/mL, $p < 0.05$) and decreased TNF-α (32 ± 4 pg/mL vs. 58 ± 6 pg/mL, $p < 0.05$) and collagen type I within the muscles (14 ± 2 % area vs. 28 ± 3 % area, $p < 0.01$), compared to the control group of rats that were allowed to rest for 7 weeks without receiving manual therapy (Barbe, Panibatla, 2021b). These studies show that manual interventions during the acute phase provide **some** inflammatory modulation. The observed decrease in collagen type I may have contributed to the prevention of fibrosis.

Furthermore, mechanical loading of neuronal tissue after injury appears to promote regeneration and improve functional outcomes. Another indication that mechanical loading of neuronal tissue after injury promotes regeneration comes from a study in which rats with median nerve injury (forearm) and inflammation showed significant improvements in muscle force tasks following treatment with manual interventions combined with High-Repetition High-Frequency (HRHF) training for 3 weeks. The interventions were applied during the sub-acute phase of nerve injury (6 to 12 weeks post-injury). Treated rats exhibited improved reach rates and impulse, with the highest scores in the group that received both HRHF training and manual interventions, compared to the untreated and HRHF-only groups. Biochemical analysis revealed that both HRHF-only and combined treatments influenced inflammatory markers, with manual interventions significantly reducing CD68 immunopositive macrophages and Degraded Myelin Basic Protein (DMBP) expression compared to HRHF-only. Electrophysiological results indicated that the HRHF-only group had higher ongoing activity in the median nerve, suggesting increased nociceptive signalling, while HRHF combined with manual interventions showed reduced nerve activity. Histological findings strongly supported these results, showing less inflammation and extracellular collagen deposition around the injured nerve in the combined treatment group. Behavioural observations **also** showed fewer discomfort-related behaviours in rats receiving the combined treatment compared to HRHF-only (Bove et al., 2019). This study suggests that manual interventions during the sub-acute phase contribute to inflammation modulation, with a decrease in intramuscular and fascial collagen deposition.

Further evidence for the beneficial effects of mechanical loading after muscle and fascia tissue inflammation is provided by the observation that mice undergoing chemical irritation to induce connective tissue inflammation showed that acute manual intervention (fascia mobilizations) on connective tissue resulted in a reduction of neutrophil infiltration (Ly-6G positive cells ($p < 0.05$), decreased expression of inducible nitric oxide synthase-2 ($p < 0.05$), and increased levels of anti-inflammatory cytokines (TGF-β1: 7.9 ± SD 1.4 vs. 4.2 ± SD 0.7 pg/mg protein, $p < 0.05$; IL-4: 5.3 ± SD.8 vs. 2.1 ± SD.4 pg/mg protein, $p < 0.05$), in comparison to no treatment (França et al., 2020). The intervention, which involved daily application of sustained pressure to the lumbodorsal skin for approximately 10 min, resulted in reduced inflammation at the back (França et al., 2020). These changes suggest that the applied manual intervention reduces inflammation by lowering NOS-2 levels, while the increase in IL-4 suggests an increase in anti-inflammatory cytokines (França et al., 2020) and promotion of myoblast fusion and differentiation (Kurosaka et al., 2023). Similarly, in rats with chemically induced inflammation, manual intervention

targeted to the lumbar fascia resulted in reduced inflammation. After 14 days of manual intervention (5 min, 3 times a week), chemokine secretion (RANTES) was significantly decreased (96.1 % reduction at <30 min post-treatment, $p < 0.002$), while neuropeptide-Y was increased approximately 3-fold immediately post-intervention ($p < 0.05$) and IL-10 showed a non-significant upward trend compared to the untreated group, indicating a shift toward anti-inflammatory and neuromodulatory response (Loghmani et al., 2021). These findings suggest that the use of manual intervention to the lumbar fascia may have an anti-inflammatory effect. The observed changes in TGF-β1, IL-4, IL-10, RANTES, neuropeptide-Y, and NOS-2 levels suggest that manual intervention on the fascia (including myofibers) may play a key role in modulating inflammatory responses.

In vitro studies have further supported the effects of mechanical stress on tissue regeneration. Shear stress applied to myoblasts increased anabolic growth factors such as IGF-1 and MGF while reducing myostatin levels and increasing nitric oxide production (Juffer et al., 2014). Mechanotransduction, the conversion of mechanical strain into biochemical signals, occurs through mechanosensitive ion channels, integrins, dystroglycan-sarcoglycans, and the glycocalyx, which regulate various signalling pathways (Van Amstel, Weide, 2025b). However, a stiffened glycocalyx may reduce membrane strain in myoblasts during shear stress, thereby potentially impairing mechanotransduction and resulting in reduced nitric oxide production, as suggested theoretically (Germain et al., 2022). While shear stress in myoblasts is essential for activating regenerative signalling, in (myo)fibroblasts it appears to suppress activity and collagen production, indicating that mechanical load **may** have cell-specific effects with therapeutic potential in fibrotic conditions (Krishnan et al., 2009, Walker et al., 2020).

In conclusion, the above-discussed results indicate that manual interventions during the (sub)acute phase offer improvement with regard to fascial and musculoskeletal tissue regeneration, but there is no direct evidence that fibrosis can be completely prevented or reversed. In our view, it is plausible that the timing, magnitude, and intensity of manual interventions are crucial for optimizing physico-chemical properties of the cell and its surroundings, which are important for local immune modulation and skeletal muscle recovery. It is expected that different types of manual stress, such as manual shear, tensile, and compression stress, with various modalities (frequency, intensity, and duration), elicit varied immunomodulatory responses. However, the optimal timing of these interventions during the phases of inflammation, proliferation, and remodelling in fascia and myofiber regeneration remains unclear. Further research is warranted to determine the optimal timing to enhance recovery and transition from hands-on manual therapy to hands-off resistance training interventions.

### 6.1. *Discussion and future directions*

Tensile and shear loads on muscle and fascia trigger immunomodulatory responses in myofibers, MuSCs, and macrophages. Manual interventions, following skin displacement principles, can enhance tissue regeneration and modulate inflammation. While animal studies show promising results, the optimal timing, intensity, and modality of manual interventions remain unclear. Future research should focus on translating these findings to humans to optimize recovery and potentially prevent fibrosis.

## 7. Discussion

Fascia adapts its biomechanical properties in response to mechanical stress. These adaptations generally occur through various processes, including structural growth and maintenance. After fascia and myofiber (micro)injury, immune cells, MuSCs, myoblasts, and (myo)fibroblasts rapidly release critical biochemical mediators that interact with the nervous system and contribute to fascia regeneration.

Immune cells such as macrophages play a critical role in the fascia and myofiber regeneration process. Macrophages actively transition from a resting, undifferentiated state into specialized functional states in response to signals from their microenvironment. Following (micro) injury, resting-state macrophages polarize into either pro-inflammatory or anti-inflammatory macrophages, a shift that is important for the effective regeneration of myofibers and fascia (Martinez et al., 2008, Vogel et al., 2014). The transition from pro-to anti-inflammatory type macrophages is vital for resolving inflammation and initiating tissue repair. However, the precise mechanisms driving this shift are still largely unclear. Some studies propose that pro-inflammatory macrophages may either revert to the resting state or undergo apoptosis (Bentzinger et al., 2013, Jain et al., 2019). These potential regulatory pathways underlying macrophage polarization remain underexplored in the literature, highlighting the need for further research to better understand the fate of pro-inflammatory macrophages during regeneration.

Mechanotransduction, as occurs during manual interventions or resistance training, effectively affects immune cells, myoblasts, and (myo)fibroblasts functioning, promoting the release of cytokines and growth factors like IL-4, IL-6, IGF-1, and MGF, which enhance fascia and myofiber regeneration (Forbes and Rosenthal, 2014). The timing, frequency, and intensity of mechanical stress are expected to be crucial for optimizing recovery; however, evidence is currently lacking.

Prolonged underloading, where tissues are subjected to insufficient mechanical stress, can significantly lead to a decrease in the ability to tolerate future stresses (Mueller and Maluf, 2002). Over time, this underloading may result in conditions like muscle atrophy (Hooijmans et al., 2023, Wesselink et al., 2024), thickening of the deep and myofascia (Kirchgesner et al., 2019; Langevin et al., 2009; Pirri, Pirri, 2023b), and adhesions between myofibers, myofascia, and deep fascia (Langevin, 2021). These adhesions can subsequently stiffen the connections between fascia and myofibers, reduce fascia–muscle shear strain, and potentially elevate tensile stress on adjacent tissues (Brandl et al., 2023, Langevin et al., 2011), thereby potentially leading to local recurrent (micro)injuries (Newell et al., 2024). Based on animal studies, fascia (micro)injury clearly affects the quality of the fascia (Bi et al., 2023; Bishop et al., 2016), increasing the risk of recurrent (micro)injury (DuBay et al., 2005) and the prolonged release of pro-inflammatory mediators (Barbe et al., 2021a). This process can lead to local immune and neuroimmune interactions, as well as alterations in neuronal excitability and pain (Yang et al., 2022).

The central challenge is determining the optimal timing and intensity of physical stress in rehabilitation programs. Current evidence, largely based on animal studies, provides limited guidance on this topic. An important point of discussion is that applying manual interventions in animals is not a straightforward task, as many factors can influence these treatments, such as the species of the animal, its condition, and the specific characteristics of the intervention itself (Bove et al., 2022). Effective movement and loading of tissues are crucial for the recovery and regeneration of myofibers and fasciae. However, it remains uncertain whether manual therapy or resistance training alone is more effective in eliciting a beneficial immune response, either locally or at the level of the nervous system. It is also unclear whether a combination of both within the same session, for example by applying manual therapy first to modulate local tissue or neural responses, followed by resistance training, might be more effective. The chosen approach can substantially impact local immune interactions, potentially influencing the resolution of inflammation and the overall effectiveness of tissue repair. Ensuring healthy fascia and myofiber recovery and regeneration is pivotal in mitigating the risk of recurrent skeletal muscle (micro)injuries, local immune and neuroimmune interactions, and eventually pain.

Although endomysium, perimysium, epimysium, and tendons are all classified as fascia, their structural and functional properties differ considerably (Schleip et al., 2012). Endomysium is a loose, three-dimensional network surrounding individual muscle fibers and

plays an adaptive, sensorimotor role, whereas perimysium organizes fascicles and distributes force across fibers, and epimysium surrounds the entire muscle primarily transmitting mechanical loads (Suarez-Rodriguez et al., 2022). Tendons are highly dense, linearly aligned, and optimized for unidirectional force transmission to bone (Purslow, 2020). These intramuscular connective tissues also differ in collagen organization, extracellular matrix composition, and mechanical behavior, confirming that findings obtained in one fascial structure cannot be generalized to all fasciae, emphasizing the need for layer-specific investigation (Purslow, 2020). In addition, chronic inflammation may lead to the accumulation of fat and collagen, as well as densification of the ground substance within fascia, which can increase tissue stiffness, impair mechanotransduction, and enhance nociceptor excitability, potentially limiting effective tissue regeneration (Van Amstel, Weide, 2025b). However, the precise mechanisms remain unclear. Human studies integrating high-resolution ultrasound elastography and shear strain models, MRI elastography, in vivo force mapping, and blood or cerebrospinal fluid (CSF) biomarker profiling are needed to monitor immune and fibrotic responses. Central neuroinflammation can be directly assessed using positron emission tomography (PET) with TSPO tracers, reflecting activation of glial immune cells, while functional MRI (fMRI) can be used to characterize functional and network-level brain alterations that may accompany or reflect neuroinflammatory processes. While our narrative review summarizes the current evidence, future work should quantify the statistical significance and effect sizes of reported findings to clarify the magnitude and reliability of observed relationships, as narrative synthesis alone may overemphasize clinically trivial effects. Further investigation is therefore urgently required to gain a deeper understanding of the biochemical processes involved in fascia and myofiber regeneration, as well as the effects of different frequencies, intensities, and durations of mechanical stress on these processes.

## 8. Conclusion

Local immune and neuroimmune interactions are crucial for fascia regeneration, with macrophages playing a central role in resolving inflammation and facilitating skeletal muscle repair. The shift from pro-inflammatory to anti-inflammatory type macrophages is critical for fascia and facilitating skeletal muscle recovery, though the precise mechanisms driving this shift remain poorly understood (Bentzinger et al., 2013). Evidence from animal and cell-based studies indicates that manual interventions (Barbe, Panibatla, 2021b; Bove et al., 2019; França et al., 2020) and mechanical stress (Huijing and Jaspers, 2005) can modulate immune function, particularly through altered secretion of biochemical mediators such as IGF-1, HGF, MGF, IL-4, IL-6, TGF-β, and IL-10 by immune cells, muscle cells, and fibroblasts. Integrative experimental and theoretical work on fascia–muscle interactions further highlights mechanical stress transmission and tissue deformation as key determinants of structural and functional adaptation (Van Amstel, Weide, 2025b). Manual interventions, such as fascia and joint mobilizations, demonstrate therapeutic potential by reducing local inflammation and fibrosis while enhancing tissue repair in animals. Specifically, IL-4 promotes muscle regeneration by stimulating myoblast differentiation. Anabolic factors like IGF-1, HGF, and MGF support muscle growth. Anti-inflammatory cytokines such as IL-10 suppress pro-inflammatory mediators like TNF. IL-6, depending on the context, can enhance anti-inflammatory signalling. Together, these factors reduce peripheral inflammation, which decreases nociceptive signalling and promotes the reduction of neuroinflammation, thereby reducing pain and promoting fascia, myofiber, and neural tissue recovery. However, the timing and intensity of these interventions during rehabilitation are critical factors influencing recovery outcomes. Although preclinical and animal studies support the benefits of these interventions, further studies are needed to establish optimal timing and dosage across different stages of rehabilitation. A deeper understanding of how to balance mechanical loading and immune modulation will be crucial for minimizing dysregulated neuroimmune interactions and maximizing tissue regeneration. In conclusion, an integrated approach that combines controlled mechanical loading with targeted immune modulation is expected to be key in facilitating effective fascia and myofiber regeneration. This is important for enhancing skeletal muscle and fascia quality and reducing the risk of chronic pain and neuroimmune dysregulation.

## CRediT authorship contribution statement

**Robbert N.van Amstel:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Ivo J. Lutke Schipholt:** Writing – review & editing, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Guido Weide:** Writing – review & editing, Validation, Formal analysis. **Annelies L. Pool-Goudzwaard:** Writing – review & editing, Supervision, Conceptualization. **Richard T. Jaspers:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

## Declaration of competing interests

The authors declare that they have no known competing financial or personal relationships that could have appeared to influence the work reported in this paper.

## References

Abdelmagid, S.M., Barr, A.E., Rico, M., Amin, M., Litvin, J., Popoff, S.N., et al., 2012. Performance of repetitive tasks induces decreased grip strength and increased fibrogenic proteins in skeletal muscle: role of force and inflammation. PLoS One 7 (5), e38359.

Bäckryd, E., Tanum, L., Lind, A.-L., Larsson, A., Gordh, T., 2017. Evidence of both systemic inflammation and neuroinflammation in fibromyalgia patients, as assessed by a multiplex protein panel applied to the cerebrospinal fluid and to plasma. J. Pain Res. 515–525.

Barbe, M.F., Amin, M., Harris, M.Y., Panibatla, S.T., Assari, S., Popoff, S.N., et al., 2022. Manual therapy facilitates homeostatic adaptation to bone microstructural declines induced by a rat model of repetitive forceful task. Int. J. Mol. Sci. 23 (12), 6586.

Barbe, M.F., Harris, M.Y., Cruz, G.E., Amin, M., Billett, N.M., Dorotan, J.T., et al., 2021a. Key indicators of repetitive overuse-induced neuromuscular inflammation and fibrosis are prevented by manual therapy in a rat model. BMC Muscoskelet. Disord. 22 (1), 417.

Barbe, M.F., Panibatla, S.T., Harris, M.Y., Amin, M., Dorotan, J.T., Cruz, G.E., et al., 2021b. Manual therapy with rest as a treatment for established inflammation and fibrosis in a rat model of repetitive strain injury. Front. Physiol. 12, 755923.

Barnig, C., Lutzweiler, G., Giannini, M., Lejay, A., Charles, A.-L., Meyer, A., et al., 2022. Resolution of inflammation after skeletal muscle ischemia–reperfusion injury: a focus on the lipid mediators lipoxins, resolvins, protectins and maresins. Antioxidants 11 (6), 1213.

Bentzinger, C.F., Wang, Y.X., Dumont, N.A., Rudnicki, M.A., 2013. Cellular dynamics in the muscle satellite cell niche. EMBO Rep. 14 (12), 1062–1072.

Bentzinger, C.F., Wang, Y.X., Rudnicki, M.A., 2012. Building muscle: molecular regulation of myogenesis. Cold Spring Harbor Perspect. Biol. 4 (2), a008342.

Berrueta, L., Muñoz-Vergara, D., Martin, D., Thompson, R., Sansbury, B.E., Spite, M., et al., 2023. Effect of stretching on inflammation in a subcutaneous carrageenan mouse model analyzed at single-cell resolution. J. Cell. Physiol. 238 (12), 2778–2793.

Bi, X., Li, B., Zou, J., Zhao, J., Chen, Y., Wang, X., et al., 2023. Fascia promotes adipose tissue regeneration by improving early macrophage infiltration after fat grafting in a mouse model. Plast. Reconstr. Surg. 152 (3), 446e-57e.

Bishop, J.H., Fox, J.R., Maple, R., Loretan, C., Badger, G.J., Henry, S.M., et al., 2016. Ultrasound evaluation of the combined effects of thoracolumbar fascia injury and movement restriction in a porcine model. PLoS One 11 (1), e0147393.

Bogdanov, J., Lan, R., Chu, T.N., Bolia, I.K., Weber, A.E., Petrigliano, F.A., 2021. Fatty degeneration of the rotator cuff: pathogenesis, clinical implications, and future treatment. JSES Rev. Rep. Techn. 1 (4), 301–308.

Bordoni, B., Escher, A.R., Tobbi, F., Pianese, L., Ciardo, A., Yamahata, J., et al., 2022. Fascial nomenclature: update 2022. Cureus 14 (6).

Bove, G.M., Chapelle, S.L., Barrigar, M.J., Barbe, M.F., 2022. Manual therapy research methods in animal models, focusing on soft tissues. Front. Integr. Neurosci. 15, 802378.

Bove, G.M., Delany, S.P., Hobson, L., Cruz, G.E., Harris, M.Y., Amin, M., et al., 2019. Manual therapy prevents onset of nociceptor activity, sensorimotor dysfunction, and neural fibrosis induced by a volitional repetitive task. Pain 160 (3), 632–644.
Brandl, A., Wilke, J., Egner, C., Reer, R., Schmidt, T., Schleip, R., 2023. Thoracolumbar fascia deformation during deadlifting and trunk extension in individuals with and without back pain. Front. Med. 10, 1155.
Brandl, A., Wilke, J., Horstmann, T., Reer, R., Egner, C., Schmidt, T., et al., 2024. Quantifying thoracolumbar fascia deformation to discriminate acute low back pain patients and healthy individuals using ultrasound. Sci. Rep. 14 (1), 20044.
Castella, L.F., Gabbiani, G., McCulloch, C.A., Hinz, B., 2010. Regulation of myofibroblast activities: calcium pulls some strings behind the scene. Exp. Cell Res. 316 (15), 2390–2401.
Chapman, M.A., Mukund, K., Subramaniam, S., Brenner, D., Lieber, R.L., 2017. Three distinct cell populations express extracellular matrix proteins and increase in number during skeletal muscle fibrosis. Am. J. Physiol. Cell Physiol. 312 (2), C131–C143.
Côté, J.A., Lessard, J., Pelletier, M., Marceau, S., Lescelleur, O., Fradette, J., et al., 2017. Role of the TGF-β pathway in dedifferentiation of human mature adipocytes. FEBS Open Bio 7 (8), 1092–1101.
De Micheli, A.J., Laurilliard, E.J., Heinke, C.L., Ravichandran, H., Fraczek, P., Soueid-Baumgarten, S., et al., 2020. Single-cell analysis of the muscle stem cell hierarchy identifies heterotypic communication signals involved in skeletal muscle regeneration. Cell Rep. 30 (10), 3583–3595. e5.
Della Pietra, A., Gómez Dabó, L., Mikulenka, P., Espinoza-Vinces, C., Vuralli, D., Baytekin, I., et al., 2024. Mechanosensitive receptors in migraine: a systematic review. J. Headache Pain 25 (1), 6.
Dort, J., Fabre, P., Molina, T., Dumont, N.A., 2019. Macrophages are key regulators of stem cells during skeletal muscle regeneration and diseases. Stem Cell. Int. 2019 (1), 4761427.
Du, H., Bartleson, J.M., Butenko, S., Alonso, V., Liu, W.F., Winer, D.A., et al., 2023. Tuning immunity through tissue mechanotransduction. Nat. Rev. Immunol. 23 (3), 174–188.
DuBay, D.A., Wang, X., Adamson, B., Kuzon, Jr WM., Dennis, R.G., Franz, M.G., 2005. Progressive fascial wound failure impairs subsequent abdominal wall repairs: a new animal model of incisional hernia formation. Surgery 137 (4), 463–471.
Fede, C., Clair, C., Pirri, C., Petrelli, L., Zhao, X., Sun, Y., et al., 2025. The human superficial fascia: a narrative review. Int. J. Mol. Sci. 26 (3), 1289.
Fede, C., Petrelli, L., Guidolin, D., Porzionato, A., Pirri, C., Fan, C., et al., 2021a. Evidence of a new hidden neural network into deep fasciae. Sci. Rep. 11 (1), 1–11.
Fede, C., Petrelli, L., Pirri, C., Neuhuber, W., Tiengo, C., Biz, C., et al., 2022. Innervation of human superficial fascia. Front. Neuroanat. 73.
Fede, C., Pirri, C., Fan, C., Petrelli, L., Guidolin, D., De Caro, R., et al., 2021b. A closer look at the cellular and molecular components of the deep/muscular fasciae. Int. J. Mol. Sci. 22 (3), 1411.
Fisher, P.W., Zhao, Y., Rico, M.C., Massicotte, V.S., Wade, C.K., Litvin, J., et al., 2015. Increased CCN2, substance P and tissue fibrosis are associated with sensorimotor declines in a rat model of repetitive overuse injury. J. Cell Commun. Signal. 9, 37–54.
Forbes, S.J., Rosenthal, N., 2014. Preparing the ground for tissue regeneration: from mechanism to therapy. Nat. Med. 20 (8), 857–869.
França, M.E.D., Sinhorim, L., Martins, D.F., Schleip, R., Machado-Pereira, N.A., de Souza, G.M., et al., 2020. Manipulation of the fascial system applied during acute inflammation of the connective tissue of the thoracolumbar region affects transforming growth Factor-β1 and Interleukin-4 levels: experimental study in mice. Front. Physiol. 11, 1517.
Generaal, E., Vogelzangs, N., Macfarlane, G.J., Geenen, R., Smit, J.H., Dekker, J., et al., 2014. Basal inflammation and innate immune response in chronic multisite musculoskeletal pain. PAIN® 155 (8), 1605–1612.
Germain, P., Delalande, A., Pichon, C., 2022. Role of muscle LIM protein in mechanotransduction process. Int. J. Mol. Sci. 23 (17), 9785.
Greenlee-Wacker, M.C., 2016. Clearance of apoptotic neutrophils and resolution of inflammation. Immunol. Rev. 273 (1), 357–370.
Haroon, M., Klein-Nulend, J., Bakker, A.D., Jin, J., Seddiqi, H., Offringa, C., et al., 2021. Myofiber stretch induces tensile and shear deformation of muscle stem cells in their native niche. Biophys. J. 120 (13), 2665–2678.
Heppenstall, P.A., Lewin, G.R., 2006. A role for T-type Ca2+ channels in mechanosensation. Cell Calcium 40 (2), 165–174.
Hillege, M.M., Shi, A., Galli, R.A., Wu, G., Bertolino, P., Hoogaars, W.M., et al., 2022. Lack of Tgfbr1 and Acvr1b synergistically stimulates myofibre hypertrophy and accelerates muscle regeneration. eLife 11, e77610.
Hilliard, B.A., Amin, M., Popoff, S.N., Barbe, M.F., 2021. Force dependent effects of chronic overuse on fibrosis-related genes and proteins in skeletal muscles. Connect. Tissue Res. 62 (1), 133–149.
Hinz, B., McCulloch, C.A., Coelho, N.M., 2019. Mechanical regulation of myofibroblast phenoconversion and collagen contraction. Exp. Cell Res. 379 (1), 119–128.
Hodges, P.W., Bailey, J.F., Fortin, M., Battié, M.C., 2021. Paraspinal muscle imaging measurements for common spinal disorders: review and consensus-based recommendations from the ISSLS degenerative spinal phenotypes group. Eur. Spine J. 1–14.
Hodges, P.W., Danneels, L., 2019. Changes in structure and function of the back muscles in low back pain: different time points, observations, and mechanisms. J. Orthop. Sports Phys. Ther. 49 (6), 464–476.
Hooijmans, M.T., Schlaffke, L., Bolsterlee, B., Schlaeger, S., Marty, B., Mazzoli, V., 2023. Compositional and functional MRI of skeletal muscle: a review. J. Magn. Reson. Imag.
Huijing, P., Jaspers, R., 2005. Adaptation of muscle size and myofascial force transmission: a review and some new experimental results. Scand. J. Med. Sci. Sports 15 (6), 349–380.
Huijing, P.A., 2009. Epimuscular myofascial force transmission: a historical review and implications for new research. International society of biomechanics muybridge award lecture, Taipei, 2007. J. Biomech. 42 (1), 9–21.
Hysing, E.-B., Smith, L., Thulin, M., Karlsten, R., Bothelius, K., Gordh, T., 2019. Detection of systemic inflammation in severely impaired chronic pain patients and effects of a multimodal pain rehabilitation program. Scandinavian J. Pain 19 (2), 235–244.
Ingber, D.E., 2006. Cellular mechanotransduction: putting all the pieces together again. FASEB J. 20 (7), 811–827.
Italiani, P., Boraschi, D., 2014. From monocytes to M1/M2 macrophages: phenotypical vs. functional differentiation. Front. Immunol. 5, 514.
Jain, N., Moeller, J., Vogel, V., 2019. Mechanobiology of macrophages: how physical factors coregulate macrophage plasticity and phagocytosis. Annu. Rev. Biomed. Eng. 21 (1), 267–297.
Ji, R.-R., Nackley, A., Huh, Y., Terrando, N., Maixner, W., 2018. Neuroinflammation and central sensitization in chronic and widespread pain. Anesthesiology 129 (2), 343–366.
Jiang, D., Christ, S., Correa-Gallegos, D., Ramesh, P., Kalgudde Gopal, S., Wannemacher, J., et al., 2020. Injury triggers fascia fibroblast collective cell migration to drive scar formation through N-cadherin. Nat. Commun. 11 (1), 5653.
Juffer, P., Bakker, A.D., Klein-Nulend, J., Jaspers, R.T., 2014. Mechanical loading by fluid shear stress of myotube glycocalyx stimulates growth factor expression and nitric oxide production. Cell Biochem. Biophys. 69, 411–419.
Kim, H.K., Park, S.K., Zhou, J.-L., Taglialatela, G., Chung, K., Coggeshall, R.E., et al., 2004. Reactive oxygen species (ROS) play an important role in a rat model of neuropathic pain. Pain 111 (1), 116–124.
Kirchgesner, T., Tamigneaux, C., Acid, S., Perlepe, V., Lecouvet, F., Malghem, J., et al., 2019. Fasciae of the musculoskeletal system: MRI findings in trauma, infection and neoplastic diseases. Insights Imaging 10, 1–12.
Kondrup, F., Gaudreault, N., Venne, G., 2022. The deep fascia and its role in chronic pain and pathological conditions: a review. Clin. Anat. 35 (5), 649–659.
Koppenhaver, S., Gaffney, E., Oates, A., Eberle, L., Young, B., Hebert, J., et al., 2020. Lumbar muscle stiffness is different in individuals with low back pain than asymptomatic controls and is associated with pain and disability, but not common physical examination findings. Musculoskeletal Sci.Pract. 45, 102078.
Kosmac, K., Peck, B.D., Walton, R.G., Mula, J., Kern, P.A., Bamman, M.M., et al., 2018. Immunohistochemical identification of human skeletal muscle macrophages. Bio-protocol 8 (12), e2883–e.
Krishnan, R., Park, C.Y., Lin, Y.-C., Mead, J., Jaspers, R.T., Trepat, X., et al., 2009. Reinforcement versus fluidization in cytoskeletal mechanoresponsiveness. PLoS One 4 (5), e5486.
Kurosaka, M., Hung, Y.-L., Machida, S., Kohda, K., 2023. IL-4 signaling promotes myoblast differentiation and fusion by enhancing the expression of MyoD, myogenin, and myomerger. Cells 12 (9), 1284.
Langevin, H.M., 2021. Fascia mobility, proprioception, and myofascial pain. Life 11 (7), 668.
Langevin, H.M., Cornbrooks, C.J., Taatjes, D.J., 2004. Fibroblasts form a body-wide cellular network. Histochem. Cell Biol. 122 (1), 7–15.
Langevin, H.M., Fox, J.R., Koptiuch, C., Badger, G.J., Greenan-Naumann, A.C., Bouffard, N.A., et al., 2011. Reduced thoracolumbar fascia shear strain in human chronic low back pain. BMC Muscoskelet. Disord. 12 (1), 203.
Langevin, H.M., Stevens-Tuttle, D., Fox, J.R., Badger, G.J., Bouffard, N.A., Krag, M.H., et al., 2009. Ultrasound evidence of altered lumbar connective tissue structure in human subjects with chronic low back pain. BMC Muscoskelet. Disord. 10 (1), 151.
Lee, J.H., Park, I.-S., Kim, J., 2024. Ultrasonographic findings of facial muscles in patients with severe facial palsy who showed no improvement for more than 3 months on acute stage. Eur. Arch. Otorhinolaryngol. 281 (4), 2001–2010.
Loghmani, M.T., Tobin, C., Quigley, C., Fennimore, A., 2021. Soft tissue manipulation may attenuate inflammation, modulate pain, and improve gait in conscious rodents with induced low back pain. Mil. Med. 186 (Suppl. ment_1), 506–514.
Maas, H., 2019. Significance of epimuscular myofascial force transmission under passive muscle conditions. J. Appl. Physiol. 126 (5), 1465–1473.
Martinez, F.O., Sica, A., Mantovani, A., Locati, M., 2008. Macrophage activation and polarization. Front. Biosci. 13 (13), 453–461.
Mauro, A., 1961. Satellite cell of skeletal muscle fibers. J. Biophys. Biochem. Cytol. 9 (2), 493.
McLain, R.F., Pickar, J.G., 1998. Mechanoreceptor endings in human thoracic and lumbar facet joints. Spine 23 (2), 168–173.
Meade, E., Garvey, M., 2022. The role of neuro-immune interaction in chronic pain conditions; functional somatic syndrome, neurogenic inflammation, and peripheral neuropathy. Int. J. Mol. Sci. 23 (15), 8574.
Mense, S., 2019. Innervation of the thoracolumbar fascia. Eur. J.Transl. Myo. 29 (3).
Miller, T., Wetter, J., Jarvis, M., Bitner, R., 2013. Spinal microglial activation in rat models of neuropathic and osteoarthritic pain: an autoradiographic study using [3H] PK 11195. Eur. J. Pain 17 (5), 692–703.
Moalem, G., Xu, K., Yu, L., 2004. T lymphocytes play a role in neuropathic pain following peripheral nerve injury in rats. Neuroscience 129 (3), 767–777.
Moratal, C., Raffort, J., Arrighi, N., Rekima, S., Schaub, S., Dechesne, C., et al., 2018. IL-1β-and IL-4-polarized macrophages have opposite effects on adipogenesis of intramuscular fibro-adipogenic progenitors in humans. Sci. Rep. 8 (1), 17005.
Morin, N., Owolabi, S., Harty, M., Papa, E., Tracy, Jr T., Shaw, S., et al., 2007. Neutrophils invade lumbar dorsal root ganglia after chronic constriction injury of the sciatic nerve. J. Neuroimmunol. 184 (1-2), 164–171.

Morris, P., Ali, K., Merritt, M., Pelletier, J., Macedo, L.G., 2020. A systematic review of the role of inflammatory biomarkers in acute, subacute and chronic non-specific low back pain. BMC Muscoskelet. Disord. 21 (1), 1–12.
Mueller, M.J., Maluf, K.S., 2002. Tissue adaptation to physical stress: a proposed "Physical Stress Theory" to guide physical therapist practice, education, and research. Phys. Ther. 82 (4), 383–403.
Newell, E., Chorney, H., Tiegs-Heiden, C.A., Benson, J.C., Ouellet, J., Driscoll, M., 2024. Augmentation of musculoskeletal soft tissue morphology within low back pain patients may suggest the presence of physiological stress shielding: an in vivo study. J. Biomech. 162, 111894.
Pan, D., Zhang, Z., Chen, D., Huang, Q., Sun, T., 2020. Morphological alteration and TGF-β1 expression in multifidus with lumbar disc herniation. Indian J. Orthop. 54, 141–149.
Pavan, P.G., Stecco, A., Stern, R., Stecco, C., 2014. Painful connections: densification versus fibrosis of fascia. Curr. Pain Headache Rep. 18 (8), 1–8.
Pereira, M.R., Leite, P.E.C., 2016. The involvement of parasympathetic and sympathetic nerve in the inflammatory reflex. J. Cell. Physiol. 231 (9), 1862–1869.
Perry, V.H., 2004. The influence of systemic inflammation on inflammation in the brain: implications for chronic neurodegenerative disease. Brain Behav. Immun. 18 (5), 407–413.
Pirri, C., Caroccia, B., Angelini, A., Piazza, M., Petrelli, L., Caputo, I., et al., 2023a. A new player in the mechanobiology of deep fascia: yes-associated protein (YAP). Int. J. Mol. Sci. 24 (20), 15389.
Pirri, C., Petrelli, L., Guidolin, D., Porzionato, A., Fede, C., Macchi, V., et al., 2024a. Myofascial junction: emerging insights into the connection between deep/muscular fascia and muscle. Clin. Anat. 37 (5), 534–545.
Pirri, C., Pirri, N., Guidolin, D., Macchi, V., Porzionato, A., De Caro, R., et al., 2023b. Ultrasound imaging of thoracolumbar fascia thickness: chronic non-specific lower back pain versus healthy subjects; A sign of a "Frozen Back". Diagnostics 13 (8), 1436.
Pirri, C., Pirri, N., Macchi, V., Porzionato, A., De Caro, R., Stecco, C., 2024b. Ultrasound imaging of thoracolumbar fascia: a systematic review. Medicina 60 (7).
Pratt, R.L., 2021. Hyaluronan and the fascial frontier. Int. J. Mol. Sci. 22 (13), 6845.
Purslow, P.P., 2010. Muscle fascia and force transmission. J. Bodyw. Mov. Ther. 14 (4), 411–417.
Purslow, P.P., 2020. The structure and role of intramuscular connective tissue in muscle function. Front. Physiol. 11, 495.
Rummens, S., Dierckx, S., Brumagne, S., Desloovere, K., Peers, K., 2024. Three-dimensional freehand ultrasonography to measure muscle volume of the lumbar multifidus: reliability of processing technique and validity through comparison to magnetic resonance imaging. J. Anat. 244 (4), 601–609.
Sanabria-Mazo, J.P., Colomer-Carbonell, A., Carmona-Cervelló, M., Feliu-Soler, A., Borràs, X., Grasa, M., et al., 2022. Immune-inflammatory and hypothalamic-pituitary-adrenal axis biomarkers are altered in patients with non-specific low back pain: a systematic review. Front. Immunol. 13, 945513.
Sandström, A., Torrado-Carvajal, A., Morrissey, E.J., Kim, M., Alshelh, Z., Zhu, Y., et al., 2022. [11C]-PBR28 positron emission tomography signal as an imaging marker of joint inflammation in knee osteoarthritis. Pain 10, 1097.
Santa-Cecília, F.V., Ferreira, D.W., Guimaraes, R.M., Cecilio, N.T., Fonseca, M.M., Lopes, A.H., et al., 2019. The NOD2 signaling in peripheral macrophages contributes to neuropathic pain development. Pain 160 (1), 102–116.
Schilder, A., Hoheisel, U., Magerl, W., Benrath, J., Klein, T., Treede, R.-D., 2014. Sensory findings after stimulation of the thoracolumbar fascia with hypertonic saline suggest its contribution to low back pain. PAIN® 155 (2), 222–231.
Schleip, R., Gabbiani, G., Wilke, J., Naylor, I., Hinz, B., Zorn, A., et al., 2019a. Fascia is able to actively contract and may thereby influence musculoskeletal dynamics: a histochemical and mechanographic investigation. Front. Physiol. 10, 336.
Schleip, R., Hedley, G., Yucesoy, C.A., 2019b. Fascial nomenclature: update on related consensus process. Clin. Anat. 32 (7), 929–933.
Schleip, R., Jäger, H., Klingler, W., 2012. What is 'fascia'? A review of different nomenclatures. J. Bodyw. Mov. Ther. 16 (4), 496–502.
Schleip, R., Klingler, W., 2019. Active contractile properties of fascia. Clin. Anat. 32 (7), 891–895.
Shan, S., Fang, B., Zhang, Y., Wang, C., Zhou, J., Niu, C., et al., 2019. Mechanical stretch promotes tumoricidal M1 polarization via the FAK/NF-κB signaling pathway. FASEB J. 33 (12), 13254–13266.
Shi, A., Hillege, M.M., Wüst, R.C., Wu, G., Jaspers, R.T., 2021. Synergistic short-term and long-term effects of TGF-β1 and 3 on collagen production in differentiating myoblasts. Biochem. Biophys. Res. Commun. 547, 176–182.
Stecco, A., Bonaldi, L., Fontanella, C.G., Stecco, C., Pirri, C., 2023. The effect of mechanical stress on hyaluronan fragments' inflammatory cascade: clinical implications. Life 13 (12), 2277.
Stecco, A., Cowman, M., Pirri, N., Raghavan, P., Pirri, C., 2022. Densification: hyaluronan aggregation in different human organs. Bioengineering 9 (4), 159.
Stecco, C., Fede, C., Macchi, V., Porzionato, A., Petrelli, L., Biz, C., et al., 2018. The fasciacytes: a new cell devoted to fascial gliding regulation. Clin. Anat. 31 (5), 667–676.
Stecco, C., Gagey, O., Belloni, A., Pozzuoli, A., Porzionato, A., Macchi, V., et al., 2007. Anatomy of the deep fascia of the upper limb. Second part: study of innervation. Morphologie 91 (292), 38–43.
Su, Y., Yin, X., 2025. The molecular mechanism of macrophages in response to mechanical stress. Ann. Biomed. Eng. 53 (2), 318–330.
Suarez-Rodriguez, V., Fede, C., Pirri, C., Petrelli, L., Loro-Ferrer, J.F., Rodriguez-Ruiz, D., et al., 2022. Fascial innervation: a systematic review of the literature. Int. J. Mol. Sci. 23 (10), 5674.
Sun, Y., Koyama, Y., Shimada, S., 2022. Inflammation from peripheral organs to the brain: how does systemic inflammation cause neuroinflammation? Front. Aging Neurosci. 14, 903455.
Talla, U., Bozonet, S.M., Parker, H.A., Hampton, M.B., Vissers, M.C., 2019. Prolonged exposure to hypoxia induces an autophagy-like cell survival program in human neutrophils. J. Leukoc. Biol. 106 (6), 1367–1379.
Tomasek, J.J., Gabbiani, G., Hinz, B., Chaponnier, C., Brown, R.A., 2002. Myofibroblasts and mechano-regulation of connective tissue remodelling. Nat. Rev. Mol. Cell Biol. 3 (5), 349.
Tomlinson, J., Zwirner, J., Ondruschka, B., Prietzel, T., Hammer, N., 2020. Innervation of the hip joint capsular complex: a systematic review of histological and immunohistochemical studies and their clinical implications for contemporary treatment strategies in total hip arthroplasty. PLoS One 15 (2), e0229128.
Torrado-Carvajal, A., Toschi, N., Albrecht, D.S., Chang, K., Akeju, O., Kim, M., et al., 2021. Thalamic neuroinflammation as a reproducible and discriminating signature for chronic low back pain. Pain 162 (4), 1241–1249.
Tu, H., Li, Y.-L., 2023. Inflammation balance in skeletal muscle damage and repair. Front. Immunol. 14, 1133355.
Van Amstel, R.N., Brandl, A., Bartsch, K., Weide, G., Jaspers, R., Pool-Goudzwaard, A., et al., 2025a. Validation of speckle tracking analysis for assessing fascia sliding mobility. J. Biomech. 182 (2025), 112580.
Van Amstel, R.N., Weide, G., Wesselink, E.O., Noten, K., Jacobs, K., Pool-Goudzwaard, A., et al., 2025b. A review and empirical findings of fasciae and muscle interactions in low back pain. Front. Physiol. 16, 30.
van Santen, V.J., Klein-Nulend, J., Bakker, A.D., Jaspers, R.T., 2022. Stiff matrices enhance myoblast proliferation, reduce differentiation, and alter the response to fluid shear stress in vitro. Cell Biochem. Biophys. 80 (1), 161–170.
Vogel, D.Y., Glim, J.E., Stavenuiter, A.W., Breur, M., Heijnen, P., Amor, S., et al., 2014. Human macrophage polarization in vitro: maturation and activation methods compared. Immunobiology 219 (9), 695–703.
Vogel, S., Magerl, W., Treede, R.-D., Schilder, A., 2022. Dose-dependent pain and pain radiation after chemical stimulation of the thoracolumbar fascia and multifidus muscle: a single-blinded, cross-over study revealing a higher impact of fascia stimulation. Life 12 (3), 340.
Walker, M., Rizzuto, P., Godin, M., Pelling, A.E., 2020. Structural and mechanical remodeling of the cytoskeleton maintains tensional homeostasis in 3D microtissues under acute dynamic stretch. Sci. Rep. 10 (1), 1–16.
Wang, T., Zhang, L., Chen, W., Long, Y., Zhang, Y., Wang, L., et al., 2025. Single-cell RNA-seq uncovers cellular heterogeneity from deep fascia in necrotizing fasciitis patients. J. Inflamm. Res. 995–1012.
Weide, G., Van Der Zwaard, S., Huijing, P.A., Jaspers, R.T., Harlaar, J., 2017. 3D ultrasound imaging: fast and cost-effective morphometry of musculoskeletal tissue. JoVE J. 129, e55943.
Wesselink, E.O., Pool-Goudzwaard, A., De Leener, B., Law, C.S.W., Fenyo, M.B., Ello, G. M., et al., 2024. Investigating the associations between lumbar paraspinal muscle health and age, BMI, sex, physical activity, and back pain using an automated computer-vision model: a UK Biobank study. Spine J.
Willard, F., Vleeming, A., Schuenke, M., Danneels, L., Schleip, R., 2012. The thoracolumbar fascia: anatomy, function and clinical considerations. J. Anat. 221 (6), 507–536.
Wynn, T.A., Vannella, K.M., 2016. Macrophages in tissue repair, regeneration, and fibrosis. Immunity 44 (3), 450–462.
Xanthos, D.N., Sandkühler, J., 2014. Neurogenic neuroinflammation: inflammatory CNS reactions in response to neuronal activity. Nat. Rev. Neurosci. 15 (1), 43–53.
Xu, G.-K., Yang, C., Du, J., Feng, X.-Q., 2014. Integrin activation and internalization mediated by extracellular matrix elasticity: a biomechanical model. J. Biomech. 47 (6), 1479–1484.
Yahia, L.H., Rhalmi, S., Newman, N., Isler, M., 1992. Sensory innervation of human thoracolumbar fascia: an immunohistochemical study. Acta Orthop. Scand. 63 (2), 195–197.
Yang, J.-X., Wang, H.-F., Chen, J.-Z., Li, H.-Y., Hu, J.-C., Yu, A.-A., et al., 2022. Potential neuroimmune interaction in chronic pain: a review on immune cells in peripheral and central sensitization. Front. Pain Res. 3, 946846.
Yang, S., Plotnikov, S.V., 2021. Mechanosensitive regulation of fibrosis. Cells 10 (5), 994.
Yang, W., Hu, P., 2018. Skeletal muscle regeneration is modulated by inflammation. J. Orthop. Transl. 13, 25–32.
Yu, X., Liu, H., Hamel, K.A., Morvan, M.G., Yu, S., Leff, J., et al., 2020. Dorsal root ganglion macrophages contribute to both the initiation and persistence of neuropathic pain. Nat. Commun. 11 (1), 264.
Zhang, H., Hong, Z., Jiang, Z., Hu, W., Hu, J., Zhu, R., 2024. miR-29b-3p affects the hypertrophy of ligamentum Flavum in lumbar spinal stenosis and its mechanism. Biochem. Genet. 1–15.
Zhao, X., Fede, C., Petrelli, L., Pirri, C., Stocco, E., Fan, C., et al., 2024. The impact of sciatic nerve injury on extracellular matrix of lower limb muscle and thoracolumbar fascia: an observational study. Life.
Zheng, L., Li, G., Cao, J., Zhao, Z., Wang, H., Dong, Q., et al., 2025. SPP1+ macrophages promote fibroblast-to-myofibroblast transformation during hypoxia in deep fascia of acute compartment syndrome. Front. Immunol. 16, 1588926.
Zimowska, M., Kasprzycka, P., Bocian, K., Delaney, K., Jung, P., Kuchcinska, K., et al., 2017. Inflammatory response during slow-and fast-twitch muscle regeneration. Muscle Nerve 55 (3), 400–409.