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## The Muscular Fascia as a Mechanobiological and Stem-Cell Compartment: An Umbrella Review of Its Biology, Pathology, Diagnostics and Therapeutics

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### Abstract

**Background:** Muscular (deep) fascia has moved from an anatomical afterthought to a candidate organ with its own resident cell types, matrix chemistry, innervation, progenitor populations and disease spectrum. The evidence base is now large but fragmented: basic mechanobiology, single-cell transcriptomics, stem-cell and regenerative science, diagnostic imaging and a very large therapeutic trial literature are reviewed almost entirely in separate silos.

**Objective:** To produce the most complete synthesis to date of the fascia literature by combining an umbrella review of published systematic reviews and meta-analyses with a structured narrative synthesis of the primary cellular, progenitor and mechanobiological evidence, and to define what is genuinely established, what is contested and what is absent.

**Methods.** We assembled an inventory of 104 review-level evidence records addressing fascia biology, fascia-related diagnoses and fascia-directed interventions, together with primary sources covering fascial histology, hyaluronan biology, innervation, force transmission, mechanotransduction, progenitor biology and tissue engineering. Every quantitative value reported here was taken from a retrieved source record; values that could not be confirmed are reported as not available rather than estimated. All references were screened for retraction, correction, editor's note or expression of concern.

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**Results:** Deep fascia is a layered composite of roughly 1 mm thickness with two to three collagen sublayers separated by hyaluronan-rich loose connective-tissue interlayers of about 43  $\mu\text{m}$ . It contains a distinct hyaluronan-producing cell, the fasciocyte, comprising approximately 30% of fibroblast-like cells, alongside telocytes, mast cells and a regionally variable and generally sparse myofibroblast population. Fascia hosts a CD201-positive multipotent progenitor that choreographs injury repair, and the muscle-associated fascial compartment hosts fibro-adipogenic progenitors that are indispensable for satellite-cell-mediated regeneration yet drive fibro-fatty degeneration when dysregulated. Both available humans deep-fascia single-cell datasets come from surgical disease and both converge on a macrophage-centred rather than myofibroblast-centred fibrotic programme. Clinically, fascial thickening replicates across imaging studies whereas reduced shear strain does not, and the palpatory diagnosis on which much of the therapeutic literature rests has an interrater kappa of 0.452. Therapeutically, no fascia-directed intervention is supported by high-certainty evidence; extracorporeal shockwave therapy is the only modality with both medium- and long-term effect in the largest network, corticosteroid effects are marginal against their own minimal important difference, and only one adequately powered placebo-controlled randomised trial of an orthobiologic in a fascial disease exists.

**Conclusion:** Fascia is best understood as a mechanically gated progenitor and immune compartment rather than as inert packing tissue. The principal obstacle to translation is not a shortage of trials but the absence of a validated case definition, a healthy human single-cell reference atlas, and any first-in-human trial of a fascia-derived cellular product.

## Keywords

Fascia; Mechanotransduction; Fibro-adipogenic progenitors; Hyaluronan; Myofascial pain; Umbrella review.

## Introduction

For most of the modern anatomical era, fascia was what had to be removed before dissection could begin. That framing has collapsed over the last two decades under the weight of three converging literatures. The first is histological and demonstrates that deep fascia is not a homogeneous membrane but a layered composite with its own resident cell types and a site-specific matrix chemistry [1]. The second is neurophysiological and demonstrates that fascia is more densely innervated than the muscle it invests and, under experimental chemical stimulation, more painful [3]. The third, and the one that motivates publication of this synthesis in a stem-cell journal, is developmental and regenerative: fascia has been shown to contain a multipotent progenitor that supplies the cells and the pre-assembled matrix of scar, and the muscle-associated fascial compartment contains the fibro-adipogenic progenitor population without which satellite cells cannot efficiently regenerate muscle [5-8].

The problem is no longer scarcity of data but fragmentation. Reviews of fascial manual therapy do not discuss fasciocyte biology; single-cell papers on fascial fibrosis do not engage with the imaging literature that defines the clinical phenotype; and the large trial literature on plantar fasciopathy and myofascial pain rarely interrogates whether the diagnostic label being treated can be applied reproducibly. We identified six existing umbrella-level products in this domain, every one organised around a single modality — needling, instrument-assisted mobilisation, rolling, cupping or photobiomodulation — or a single diagnosis, most often plantar fasciitis [9-14]. To our knowledge no synthesis integrates fascial cell and progenitor biology, anatomical continuity, matrix chemistry, diagnostic reliability and the full therapeutic review base within a single evidentiary frame.

This review sets out to do that. Its organising claim is that fascia is most usefully understood as a mechanically gated progenitor and immune compartment: a tissue whose resident stromal and

progenitor cells read mechanical and chemical state through a conserved transduction axis, and whose diseases are the pathological settings of that axis. We hold that claim to the same evidentiary standard as the therapeutic literature, distinguishing mechanism from outcome, regulatory designation from demonstrated efficacy, and absence of evidence from evidence of absence.

## Materials and Methods

### Design and reporting

This is an umbrella review — a systematic review of systematic reviews and meta-analyses — combined with a structured narrative synthesis of primary evidence in domains where review-level evidence does not yet exist, principally fascial cell biology, progenitor biology and tissue engineering. The hybrid design is deliberate and is itself a finding: the therapeutic literature is review-saturated while the biological literature is not yet review-ready.

### Evidence sources and eligibility

Searches covered MEDLINE/PubMed, publisher platforms and registry records, together with regulatory databases of the United States Food and Drug Administration, the European Medicines Agency and Health Canada. Review-level records were eligible if they were systematic reviews, meta-analyses, network meta-analyses, scoping reviews with a stated search strategy, or umbrella reviews addressing fascia biology, a fascia-related diagnosis or a fascia-directed intervention. Primary records were eligible for the narrative strand if they reported original human or animal data on fascial anatomy, histology, cell populations, matrix composition, innervation, force transmission, mechanotransduction, progenitor biology or fascial tissue engineering. Protocols without results and reviews without a reproducible search strategy were flagged as non-systematic rather than counted as review-level evidence.

### Data handling and verification rules

Three rules governed extraction. Every quantitative value reported here was taken from a retrieved source record; values that could not be confirmed are reported as not available rather than estimated, which applies to several parameters a reader might expect, including matrix metalloproteinase, tissue inhibitor and interleukin-6 concentrations in human deep fascia. Every included reference was screened for retraction, correction, editor's note or expression of concern.

That screen returned material results, stated here rather than buried. One paper is retracted and is not cited anywhere in this review for any claim: a 2012 report on Dupuytren stem cells, retracted in 2025. One further Dupuytren paper carries an expression of concern and is likewise not used. A lysyl-oxidase and stiffness paper widely cited in the mechanobiology literature carries an Editor's Note and is used only for the general principle of crosslinking-dependent stiffening [15]. Two foundational papers carry author corrections which do not affect the science and which are cited alongside the primary record: the CD201-positive fascia progenitor paper [5,16] and the interstitium paper [17].

### Quality appraisal

Where included reviews reported AMSTAR-2 or GRADE assessments, those are carried forward verbatim and reported alongside effect estimates, because in this field the certainty rating frequently contradicts the headline effect size.

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## Ethics and transparency

This work is a review of previously published literature. It involved no human participants, no identifiable human data and no animal experimentation, and therefore did not require approval by a research ethics committee or institutional review board; under Brazilian National Health Council Resolutions 466/2012 and 510/2016 such reviews fall outside the scope of mandatory ethics review. Artificial-intelligence tools assisted with literature retrieval, reference formatting and language editing; all scientific content and interpretation are the responsibility of the author.

## Results

### What fascia is: three definitions that are not interchangeable

Any complete review must begin by conceding that the field does not share one definition. Terminologia Anatomica, adopted by the fortieth edition of Gray's Anatomy, treats fasciae as dissectible sheets and recognises no body-wide system [19]. The Fascia Research Congress deliberately widened the term to a tissue type encompassing all collagenous soft connective tissues [20]. The FASCIA Nomenclature Committee ran a three-round Delphi process with 21 experts and produced two complementary definitions rather than one: a structural definition of a fascia as a dissectible aggregation of connective tissue, and a functional definition of the fascial system as a three-dimensional continuum spanning adipose tissue, aponeuroses, epineurium, joint capsules, ligaments, meninges, retinacula, tendons and all intramuscular connective tissues [19]. A recent organ-based proposal reframes the system as four anatomical organs — superficial, musculoskeletal, visceral and neural fascia — each built from two recurring layer types, one collagenous and stiff, one hyaluronan-rich and viscous [21]. That two-layer formulation is the most useful bridge from histology to function and is the one adopted here.

The consequence for appraisal is not cosmetic: a trial recruiting on “myofascial pain”, a histology study of “deep fascia” and a meta-analysis of “fascial manual therapy” may not describe the same tissue, and heterogeneity attributed to method may in part be heterogeneity of referent.

### Architecture and quantitative morphology

Across 72 human limb specimens, deep fascia averaged approximately 1 mm in thickness and comprised two to three layers of densely packed parallel collagen bundles of differing fibre orientation, separated by loose connective tissue; nerve fibres were present in every specimen [1]. In ten crural fascia dissections, mean total thickness was 924  $\mu\text{m}$  across three collagenous sublayers averaging 277.6  $\mu\text{m}$ , separated by loose interlayers of 43  $\mu\text{m}$ , with anisotropic behaviour and crimped collagen [22]. Deep fascia divides histologically into aponeurotic fascia — thick, multilayered, poorly adherent to muscle, as in the fascia lata, crural fascia, thoracolumbar fascia and rectus sheath — and epimysial fascia, thinner, elastin-rich and intimately adherent to muscle; elastic fibres constitute roughly 15% of epimysial fascia versus less than 1% of aponeurotic fascia [1].

Superficial fascia is thinner, and measurement modality matters: ultrasound systematically overestimates it, giving 420–520  $\mu\text{m}$  at the thigh against  $146.6 \pm 31.5 \mu\text{m}$  by histology, although the two correlate at  $r = 0.918$  [23]. Fascial thickness correlates with body mass at Kendall tau 0.45–0.75 [2], and a systematic review of 38 thoracolumbar ultrasound studies identified L2–L3 as the optimal assessment level [24].

Aging changes fascia in opposite directions in different regions, which is one reason that pooled “fascial stiffness” constructs mislead: lower-limb fascial thickness decreases by 12.3–25.8% with age while low-back fascial thickness increases by 40.0–76.7% [2,25]. In aged mice, whole-muscle collagen rose from  $2.95 \pm 0.46\%$  to  $9.29 \pm 0.81\%$  while hyaluronan-binding-protein optical density fell — more collagen and less hyaluronan around proprioceptors with age [26].

### **Resident cells: the fasciocyte and its neighbours**

The single most consequential cell-biological advance in this field is the identification of the fasciocyte. Formally characterised in 2018 as a cell devoted to the regulation of fascial gliding, fasciocytes are rounder and shorter-processed than classical fibroblasts, cluster along the loose connective-tissue surfaces of the collagen sublayers, stain with Alcian blue and anti-hyaluronan-binding protein, are vimentin-positive, CD68-negative and S100A4-positive, and express HAS2 messenger RNA, identifying them as the principal local hyaluronan producers [27]. They constitute approximately 30% of the fibroblast-like cells of deep fascia [2].

Electron microscopy of human fascia lata identified telocytes with a mean cell-body diameter of  $9.39 \pm 3.26 \mu\text{m}$  and telopodes up to about  $22 \mu\text{m}$ ; per field, tissue contained 3–6 fibroblasts, 0–4 mast cells, 0–2 myofibroblastic cells and 0–2 telocytes [29]. CD34-positive stromal cells and telocytes are proposed as a distributed tissue reserve and principal source of mesenchymal cells [30], and telocytes have been described in human skeletal muscle and in fibrotic settings [31–33]. Whether they are a distinct lineage or a morphological state of fibro-adipogenic progenitors remains unresolved.

Mast cells are present at  $20.4 \pm 9.4$  per square millimetre in human superficial fascia, with  $51 \pm 9.7\%$  lying among collagen fibres and about a quarter in close relation to nerve fibres — an anatomical substrate for neurogenic inflammation [23,34]. Myofibroblast density, by contrast, is low and strongly regional: median 1.52% in lumbar fascia against 0% in both plantar fascia and fascia lata, with  $H(2) = 14.0$ ,  $p < 0.01$  [2,35].

That regional distribution disciplines the contractility hypothesis. Fascia contracts in vitro in response to the thromboxane analogue U46619, caffeine and angiotensin II, with blockade by cytochalasin D, SQ-29548 and the Rho-kinase inhibitor Y-27632 [35]. Contractions over seconds to minutes are too weak to contribute to joint stability, whereas sustained changes over days to months can produce contracture [37]. The autonomic link is plausible given that roughly 40% of fascial innervation is postganglionic sympathetic [2,38]. But contractility is a regional, not a general, property.

### **Single-cell transcriptomics: fascial fibrosis is macrophage-centred**

Only two single-cell datasets of human deep fascia exist, and both come from surgical disease. In acute compartment syndrome, six patients yielded 53,116 cells after quality control, resolving fibroblasts, endothelial cells, smooth-muscle cells, mast cells, myeloid, T and B cells and cycling cells [39]. In gluteal muscle contracture, 14 fascial samples yielded 86,159 cells; fibroblasts comprised  $66.8 \pm 17.7\%$  and macrophages  $8.5 \pm 7.0\%$  of cells, with macrophages strongly enriched in disease at  $11.2 \pm 6.6\%$  versus  $1.8 \pm 1.0\%$  in controls, and a mean fibroblast–macrophage transmission-electron-microscopy separation of  $17.5 \pm 12.7 \mu\text{m}$  [41].

The critical negative finding is that alpha-smooth-muscle-actin-positive, COL1A1-positive myofibroblasts were not significantly upregulated in gluteal muscle contracture [41]. Fascial fibrosis, at least in that disease, need not be myofibroblast-driven. A convergent observation across both datasets is the appearance of an SPP1-expressing macrophage population in acute compartment syndrome and in gluteal contracture alike [39,41], suggesting a shared myeloid axis of fascial fibrosis that has not, to our knowledge, been previously assembled as a single claim. The same theme recurs in the frozen-shoulder capsular atlas, where MERTK-low CD48-positive macrophages are separated from MERTK-positive LYVE1-positive MRC1-positive resolving macrophages, alongside DKK3-positive and POSTN-positive fibroblast states [42].

No healthy-donor single-cell atlas of human muscular fascia has been published. This is the single most consequential gap in the biology of the field, because every cellular claim about “normal” fascia is currently inferred from diseased or adjacent tissue.

### **Fascia as a progenitor and stem-cell compartment**

This is the section that justifies reading fascia as a regenerative organ rather than as packing.

The fascia progenitor of wound repair. Deep scars are not built cell-by-cell at the wound site; pre-assembled fascial matrix is dragged upward into the wound, a mechanism demonstrated in 2019 and subsequently dissected molecularly [6]. The migratory machinery involves N-cadherin-dependent swarming [43], connexin-43 [44] and p120 catenin [45]. The cell responsible is a CD201-positive multipotent fibroblast progenitor resident in fascia, which generates pro-inflammatory fibroblasts and myofibroblasts in a spatiotemporally tuned sequence, with retinoic-acid and hypoxia signalling acting as entry checkpoints into the pro-inflammatory and myofibroblast states respectively [5,16]. A parallel lineage framework distinguishes Engrailed-1-positive, CD26-positive fibroblasts as the fibrogenic lineage [46], with mechanical tension activating Engrailed-1 through YAP and verteporfin reversing it [47], and Engrailed-1 small-interfering-RNA nanoparticles subsequently tested as an antifibrotic strategy [48]. A 2026 wave of pharmacological screens has begun to target this programme directly with repurposed agents including fluvastatin, thiostrepton and fenbendazole [49], tariquidar, terfenadine and zinc pyrithione [50], and FOSL1/MMP3 blockade with SR11302 [51]. A significant negative result deserves equal billing: adipocytes do not convert to myofibroblasts in this system [52].

Fibro-adipogenic progenitors. The muscle-associated fascial compartment hosts PDGFR $\alpha$ -positive, Sca1-positive fibro-adipogenic progenitors that are required for efficient satellite-cell-mediated regeneration but that produce fibro-fatty degeneration when dysregulated [7,53]. Subsequent work resolved Tie2 and Vcam1 subsets [54], identified Hic1 as a quiescence determinant [55], and established that muscle connective-tissue fibroblasts and fibro-adipogenic progenitors are the same population [56]. Macrophage-derived tumour necrosis factor drives their apoptosis whereas transforming growth factor beta-1 sustains them, with nilotinib shifting the balance [58-60]. Recent additions include RUNX2 and the CADD522 axis [61], chimeric-antigen-receptor T-cell targeting of fibro-adipogenic progenitors [62], and lysophosphatidic-acid-driven YAP/TAZ activation after denervation [63].

The fascial matrix as a satellite-cell niche. Collagen VI is required for satellite-cell self-renewal [64],

substrate elasticity near 12 kPa preserves stemness [65], laminin remodelling licenses expansion [66], collagen V signalling through the calcitonin receptor maintains quiescence [67], fibronectin loss impairs aged satellite cells [69], and fibro-adipogenic-progenitor-derived WISP1 declines with age [70]. The niche, in other words, is fascial matrix.

Fascia-derived cells as a therapeutic source. Fascia-derived cells display chondrogenic capacity [71]; superficial-fascia adipose tissue yields a higher CD105-positive fraction than deep adipose tissue [72]; fascia-derived stem cells outperform adipose-derived stem cells in an HMOX1–HIF-1 $\alpha$ -dependent manner [73]; and fascial adipocytes are functionally distinct from subcutaneous adipocytes [74]. A systematic review screened 648 records and included 34 studies — 17 in vitro, 17 animal and 4 clinical — reporting matrix remodelling as a central outcome in 81% of in vitro studies, immunomodulatory or antifibrotic effects in 56%, and functional improvement or graft integration in 82% of clinical studies, which were typically smaller than 50 patients [75]. The honest reading is that the clinical strand is entirely uncontrolled: the regenerative promise of fascia is at present biologically substantiated and clinically untested.

Tissue engineering and grafts. Decellularised porcine musculofascial matrix has been characterised [76], and a key methodological finding is that gamma irradiation at or above 25 kGy, rather than decellularisation itself, damages crosslinks in human fascia lata, reducing mechanical properties by 29.4% [77]. Adipose-derived stem cells have been used to build fascia equivalents [78], laminated collagen with alginate-encapsulated mesenchymal stromal cells tested for hernia repair [79], endometrial mesenchymal stromal cells seeded on gelatin mesh [80], and amniotic-fluid stem-cell meshes reported [81]. Clinically, fascia lata allograft abdominal-wall reconstruction produced no recurrence in 21 patients [82]; acellular dermal matrix augmentation gave intact rotator cuffs in 85% versus 40% of controls [83]; autologous fascia lata augmentation gave a 7.1% five-year retear rate [84]; and 94.9% of 39 superior-capsular-reconstruction donors were satisfied [85].

### **Matrix chemistry: hyaluronan, viscosity and the densification construct**

Hyaluronan content in human fascia tracks the sliding demand of the site. In 15 patients, retinacula of the ankle contained approximately 90  $\mu\text{g/g}$ , fascia lata approximately 35  $\mu\text{g/g}$ , rectus sheath approximately 29  $\mu\text{g/g}$  and fascia overlying trapezius and deltoid only approximately 6  $\mu\text{g/g}$ , with no significant differences by age or sex except in plantar fascia [86]. HAS1 and HAS2 generate high-molecular-weight chains of  $2\text{--}4 \times 10^6$  Da while HAS3 generates  $0.4\text{--}2.5 \times 10^5$  Da, and fascia reports chains of  $10^6\text{--}10^7$  Da [88]. Molecular weight determines receptor usage: high-molecular-weight hyaluronan signals mainly through CD44, low-molecular-weight through RHAMM, and 4–25 kDa fragments act as danger signals [89].

The rheology explains why small compositional shifts matter disproportionately: above the coil-overlap concentration, viscosity varies with the third to fourth power of concentration [91]. Above 40 °C the superstructure breaks down and viscosity falls, whereas the fall in muscle pH to approximately 6.60 after strenuous exercise is reported to raise viscosity by approximately 20% [88,92].

“Densification” denotes a reversible rheological alteration in which interlayer hyaluronan aggregates and

becomes adhesive rather than lubricating, increasing gliding resistance without a change in collagen architecture; fibrosis denotes an actual change in matrix composition [92]. The evidence for densification is rheological, imaging-based and therapeutic rather than histological: no retrieved source provides direct histological confirmation in humans [88]. Hyaluronidase, the pharmacological corollary, has improved stiffness and range of motion in post-stroke arm stiffness with effects lasting over three months [88,90,94], but the clinical literature remains uncontrolled, including a three-patient Ledderhose series [95].

### **Innervation, nociception and the limits of the proprioceptive claim**

A systematic review screening 5210 records and including 23 studies established the density comparison that anchors this field: thoracolumbar fascia contains  $3.4 \pm 0.6$  nerve fibres per  $40,000 \mu\text{m}^2$  against  $1.0 \pm 0.1$  in latissimus dorsi muscle, an approximately threefold difference, and masseter fascia  $404.5$  fibres/ $\text{mm}^2$  against masseter muscle  $227.6$  fibres/ $\text{mm}^2$  [3]. Free nerve-ending density is  $9.01 \pm 0.98\%$  in thoracolumbar fascia versus  $2.78 \pm 0.6\%$  in gluteal fascia, and approximately 40% of fascial innervation is sympathetic [2].

The proprioceptive claim requires qualification that is frequently omitted. In 20 human upper limbs sampled at five sites, deep fascia showed free nerve endings and encapsulated Ruffini and Pacini corpuscles, with the flexor retinaculum the most innervated element [96]. But corpuscular endings were not found in rat or human thoracolumbar fascia [38], and thoracolumbar fascia and fascia lata are reported to contain no Pacini or Ruffini corpuscles [2]. “Fascia is a proprioceptive organ” is therefore a site-specific statement, defensible for retinacula and not demonstrated for the thoracolumbar fascia around which most clinical theory is built. Piezo2 is the principal proprioceptive channel, present in all sampled muscle spindles and Golgi tendon organs, with 81% of parvalbumin-positive dorsal-root-ganglion neurons Piezo2-positive [97].

Nociceptive architecture is layer-specific: in rat and human thoracolumbar fascia the middle layer is largely free of free nerve endings, calcitonin-gene-related peptide is the commonest peptide, and approximately 45% of free nerve endings are low-threshold [38,98]. In human volunteers, 5.8% hypertonic saline injected into the posterior layer of thoracolumbar fascia produced significantly greater pain than injection into subcutis ( $p < 0.01$ ) or muscle ( $p < 0.001$ ) [4], replicated in a dose–response study in which peak pain was approximately 86% higher and pain area approximately 65% larger for fascia than muscle [99]. Nerve growth factor injected into erector spinae fascia caused no acute pain but produced mechanical sensitisation for a week and proton-evoked pain for two weeks without altering heat thresholds [100]. Centrally, muscle inflammation raised the proportion of fascia-responsive dorsal-horn neurons from 4% to 15%, a mechanism by which fascia becomes painful secondary to muscle pathology [101].

### **Force transmission and the myofascial chain literature**

Huijing’s taxonomy distinguishes myotendinous, intramuscular, intermuscular and extramuscular myofascial force transmission, the last two grouped as epimuscular myofascial force transmission [103]. In humans, active stretch produced 22% greater plantarflexion force and smaller relative displacement between soleus and lateral gastrocnemius aponeuroses than passive stretch [105].

The chain literature is where the field's marketing most exceeds its evidence, and the most rigorous appraisal — 62 studies from 6589 records — grades it transition by transition [106]. The superficial back line, back functional line and front functional line have all verified transitions and strong evidence; the spiral line verifies 5 of 9 and the lateral line 2 of 5; the superficial front line has zero verified transitions across 7 studies [106]. A companion review of intermuscular force transmission included 9 studies with sample sizes of 6–37 [107], and a scoping review of 20 studies covering 405 patients found the literature heterogeneous and of low methodological quality [108]. Anatomical continuity is well documented for some chains and absent for others; functional force transfers in vivo rests on low-quality evidence.

### **Mechanotransduction: the axis that unifies the field**

Integrins are the primary force sensors, with single-integrin forces of 1–40 pN and a talin rod containing 11 force-exposed vinculin-binding sites [109]. Physiological strains are small — 5–6% in human wrist tendon, 4–5% in ligament — and loading activates immediate-early genes before late matrix genes [110]. Cyclic stretch upregulates Piezo1, which promotes fibroblast activation via YAP [111]. In lung fibroblasts, 45 of 86 stiffness-enhanced transcripts overlapped YAP targets, normal shear modulus was 0.59 kPa against 5.16 kPa in fibrosis, and YAP/TAZ knockdown reduced collagen production, proliferation and traction force — a stiffness-to-YAP/TAZ-to-fibrosis feed-forward loop [112]. Latent transforming growth factor beta-1 is activated mechanically rather than only transcriptionally: myofibroblast-derived matrix released 36% of its active cytokine on contraction versus 11% for fibroblast-derived matrix [113].

Three lines of evidence bring this axis into fascia itself. First, in human thoracolumbar fascia explants, extracorporeal shockwave exposure increased YAP and phosphorylated YAP ( $p = 0.0022$ ) together with COL1A1 and HABP2 expression [114]. Second, angiotensin II activates YAP in fascial cells, and fascia expresses renin–angiotensin receptors at  $300.2 \pm 317$  copies per 25 ng for AT1R,  $147 \pm 122$  for AT2R and  $37.1 \pm 39.6$  for MasR [115]. Third, low-dose dihydrotestosterone at 0.4 ng/mL increased collagen I from  $2.09 \pm 0.91\%$  to  $4.80 \pm 1.75\%$  and decreased collagen III from  $10.46 \pm 0.53\%$  to  $3.32 \pm 0.46\%$  in a non-monotonic fashion [117]. Fascia is therefore hormonally and mechanically tunable in vitro.

Langevin's series supplies the manual-therapy mechanism. Needle rotation produces dose-dependent, non-monotonic fibroblast cytoskeletal remodelling [118]; approximately 80% of acupoints correspond to connective-tissue planes [119]; needle grasp is measurable [120]; and remodelling is blocked by blebbistatin and Rho-kinase inhibition [121]. Tissue stretch alone expands fibroblasts within minutes and is blocked by Y-27632, suramin, apyrase, octanol and carbenoxolone, implicating Rho-kinase-dependent remodelling driven by ATP released through gap-junction-like pathways [122]. Stretch is also anti-inflammatory: in rats it reduced inflammatory-lesion thickness and neutrophil counts and raised intralesional resolvin D1, an effect reproduced by resolvin injection [123].

### **Clinical phenotypes and the case-definition problem**

Reported prevalence of myofascial pain syndrome ranges from 37% of men and 65% of women aged 30–60, to 85% above age 65, to 93% in specialist pain clinics [87,124]. That dispersion is not sampling noise; it reflects the absence of a validated case definition. The measurement that constrains everything downstream is the interrater reliability of trigger-point palpation, pooled at kappa 0.452 (95% CI 0.364–0.540) across 6 studies and 363 patients [125]. A trenchant critique holds that the trigger-point construct

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is not scientifically sustainable [126], answered by an equally direct rebuttal [127]; this review presents the dispute as unresolved rather than adjudicating it.

Objective correlates exist but do not rescue the diagnosis. Microdialysis at active trigger points found elevated bradykinin, substance P, calcitonin-gene-related peptide, tumour necrosis factor alpha and interleukins 1 $\beta$ , 6 and 8 with lowered pH — and, critically, the same milieu at a remote uninvolved gastrocnemius site, implying a central component [128]. Ultrasonographically, active trigger points measure  $0.57 \pm 0.20 \text{ cm}^2$  versus latent  $0.36 \pm 0.16$  and normal  $0.17 \pm 0.22 \text{ cm}^2$ , area under the curve 0.9, although pressure-pain threshold did not correlate with area [130]. A systematic review of 33 imaging studies found no computed-tomography, positron-emission or single-photon studies at all [132].

Low back pain. Point prevalence is 18.3% and cases are projected to reach 843 million by 2050 [133]. Perimuscular connective tissue is approximately 25% thicker and more echogenic in chronic low back pain, correlating with body mass index at  $r = 0.66$  [134], and thoracolumbar fascia measures  $2.11 \pm 0.65 \text{ mm}$  versus  $1.75 \pm 0.85 \text{ mm}$  in controls [135]. Shear strain, however, does not replicate: it was lower in low back pain in a 121-subject study ( $56.4 \pm 3.1\%$  versus  $70.2 \pm 3.6\%$ ,  $p < 0.01$ ) [136] but higher in a 60-subject study ( $327.1 \pm 106.0$  versus  $290.2 \pm 99.8$ ,  $p < 0.0001$ ) [137]. A 2026 meta-analysis resolves the pattern in favour of thickness: standardised mean difference 0.64 (0.41–0.88) across 14 studies and 1001 participants for thickness, with stiffness at 0.82 [133]. Thickening replicates; shear strain does not.

Plantar fasciopathy. Incidence is 3.83 per 1000 person-years with a peak at 40–60 years [138]. The defining histology is myxoid degeneration without inflammation in 50 specimens — hence “fasciosis” rather than “fasciitis” [140]. The only pooled risk factor across 51 studies and 104 candidate variables is body mass index above  $27 \text{ kg/m}^2$ , odds ratio 3.7 (2.93–5.62) [141]. Fascia is 2.16 mm thicker (1.60–2.71) across 23 studies [142], a 4 mm cutoff gives an area under the curve of 0.950 [143], and combining thickness of  $4.05 \pm 0.74 \text{ mm}$  with a Young’s modulus of  $55.92 \pm 11.13 \text{ kPa}$  against  $100.29 \pm 58.44 \text{ kPa}$  in controls raises the area under the curve to 0.973 [144]. Elastography meta-analysis gives a standardised mean difference of  $-3.00 \text{ m/s}$  [145]. Natural history is worse than commonly stated: 44.0% of 174 patients remained symptomatic at 15 years [146].

Dupuytren disease. Prevalence rises from 12% at age 55 to 21% at 65 and 29% at 75 [147], with a global pooled estimate of 8.2% and 34.1% in type 1 diabetes [148]. Heritability is approximately 80% with a sibling recurrence risk ratio of 4.48 [149], and genome-wide association identified 9 loci of which 6 are Wnt-related, SFRP4 reaching odds ratio 1.98 at  $p = 5.6 \times 10^{-39}$  [150]. The stem-cell strand must be read with care: viable findings include CD13/CD29-positive nodular cells [151], a CD34-negative CD73/CD90/CD105-positive perinodular fat population [152] and OCT4/NANOG/STAT3/SALL4 expression in CD34-positive microvessels [153], but one prominent paper in this series is retracted and another carries an expression of concern, and neither is cited here.

Other fascial diseases. Necrotising fasciitis incidence rose from 9 to 21 per million between 2002 and 2017 with 16% mortality [154]. Fasciotomy for chronic exertional compartment syndrome succeeds in only 48% at 12 months [156]. Adhesion burden remains substantial, with 3.5% directly adhesion-related readmission at five years across 72,270 patients and a hazard ratio of 0.68 favouring laparoscopy [157];

chronic post-hernia pain affects 17.01% [158] and post-caesarean pain 15.4% [159]. Fascia also behaves as a systemic target organ: in 344 adolescents with diabetes, plantar fascia thickening predicted retinopathy (odds ratio 2.4) and autonomic neuropathy (odds ratio 4.94) [160], and in systemic sclerosis magnetic resonance imaging showed fasciitis, synovitis or subcutaneous thickening in 16 of 18 patients [161]. Delayed-onset muscle soreness appears disproportionately fascial in origin [162], although pressure-pain threshold did not change significantly in a controlled study [163].

### **Diagnostic reliability, which determines what any trial can measure**

Intra-rater intraclass correlation for deep-fascia thickness across 10 anatomical sites ranged 0.677–0.975 and inter-rater 0.473–0.966 [164]. Thoracolumbar fascia shear-wave elastography achieves intra-rater intraclass correlation of 0.86–0.94 and inter-rater 0.90–0.94 with a minimal detectable change below 4.71 kPa [165], but a dedicated multi-site reliability study reported intra-day intraclass correlations as low as 0.33 and inter-day as low as 0.54, with skin and fascia measured more reliably than muscle [166]. In plantar fasciitis, elastographic reliability was only fair to moderate at 0.42–0.64 [167]. Absolute kilopascal values are therefore not transferable between devices or laboratories, and elastography should not serve as a primary endpoint.

Interpretation also requires the right yardstick. For low back pain, the minimal important change is approximately 15 mm on a visual analogue scale and 10 points on the Oswestry Disability Index [168]. For plantar heel pain it is considerably smaller, –8.5 mm for average pain and –19.2 mm for first-step pain [170], so effect sizes cannot be transported between the two conditions.

### **Umbrella synthesis of fascia-directed interventions**

**Manual and instrument-assisted therapies:** Myofascial release improves disability in chronic low back pain with a standardised mean difference of –0.35 (–0.68, –0.02) but does not significantly improve pain at –0.12 [172], and an independent synthesis found effects below the minimal clinically important difference [174]. Massage does not change myotendinous stiffness, standardised mean difference –0.17 [175]. The most informative recent study is a quantitative-ultrasound randomised trial in which chiropractic manipulation and massage both reduced thoracolumbar fascia shear strain ( $\beta = -16\%$ ,  $p = 0.021$  and  $\beta = -32\%$ ,  $p < 0.001$ ) against a 19% increase in controls — yet the change did not correlate with disability ( $p = 0.261$ ,  $p = 0.054$ ) [176]. Mechanism moved; outcome did not follow.

Instrument-assisted soft-tissue mobilisation beats sham but has never beaten conventional physiotherapy, and the two meta-analyses disagree on certainty: pain standardised mean difference 0.60 at moderate certainty in one [177] against very low certainty in the other, function non-significant at –0.28 [10]. Foam rolling improves range of motion (effect size 0.823) without improving performance or altering stiffness [178–180]; percussive devices impaired 20-metre sprint performance ( $d = 0.34$ ) [181]. Static stretching reduces deep fascia stiffness ( $d = 0.42$ ) whereas dynamic stretching does not [182]. High-load strength training gave a 29-point Foot Function Index advantage at 3 months that had disappeared by 12 months [183].

**Needling and hydrodissection:** Dry needling produces a large short-term effect, standardised mean difference –1.91, but shows no advantage over physical modalities and all eight contributing randomised

trials carried high risk of bias [184]; an umbrella review of 36 systematic reviews covering 24,869 participants reached similarly guarded conclusions [9]. Adverse events are common but minor, from 0 to 48.15%, with major events from 0 to 0.43% [185]. Hydrodissection with 5% dextrose shows a volume dependency — 4 mL outperformed 1–2 mL to 12 weeks but the difference vanished by 24 weeks [186] — and dextrose outperformed saline (mean difference  $-1.30$ ) and corticosteroid ( $-0.81$ ) [187], ranking best on SUCRA in a network meta-analysis [188]. Fascial plane blocks provide independent anatomical proof that injectate spreads along fascial planes [189].

**Energy-based modalities:** Extracorporeal shockwave therapy outperforms placebo, with a pooled standardised mean difference of  $-0.60$  across 22 trials and 2299 participants, but at low to very low certainty and with no intensity setting beating placebo for function [191]. Focal shockwave gave a pooled effect of  $-2.818$  elsewhere [192], radial shockwave was not superior to other electrophysical modalities [193], and in a 236-study network covering 15,401 patients shockwave was the only modality effective at both medium and long term (long-term mean difference  $-2.49$ ) [194]. Photobiomodulation reduced pain by  $-22.02$  alone and outperformed shockwave by  $-20.94$  [12,195]. Therapeutic ultrasound is negative [197], and cupping rests on very low certainty with 4 of 5 trials at high risk of bias [11,198].

**Injectables:** The Cochrane review of corticosteroid injection for plantar heel pain covered 39 studies and 2492 participants and found a mean difference of  $-6.38$  ( $-11.13$ ,  $-1.64$ ) against a minimal important difference of 8, with no medium-term effect [199]; among reported rupture cases, 130 of 155 had received prior steroid [200]. Botulinum toxin ranks well for short-term pain in networks [201] but a recent meta-analysis concluded it is explicitly not recommendable for neck and shoulder myofascial pain, with a mean difference of  $-10.22$  on a 0–100 scale [203]. Prolotherapy acts slowly and durably (weighted mean difference  $-41.72$  against saline, low certainty) [204]. Foot orthoses give a standardised mean difference of  $-0.27$  [205], and low-dye taping estimates diverge markedly,  $-1.24$  [206] against  $-3.60$  [194], a discrepancy we flag rather than average.

**Orthobiologics:** Platelet-rich plasma is superior to corticosteroid between 3 and 12 months, but 9 of 15 contributing trials carried high risk of bias [207], and a meta-analysis of 24 randomised trials with 1653 participants found better pain scores at 3–6 months with no difference in fascial thickness [208]. Subfascial platelet-rich plasma in greater trochanteric pain syndrome outperformed control on the Hip Outcome Score sports subscale, 32.09 versus 20.52,  $p = 0.048$  [209]. Amniotic and placental products supply the strongest single dataset: after a Level I pilot [210], a 145-patient, 14-site randomised trial of micronised dehydrated human amnion–chorion membrane reported a 76% versus 45% reduction in visual analogue scale pain ( $p < 0.0001$ ) and a 60% versus 40% improvement in the revised Foot Function Index ( $p = 0.0004$ ) [211], although an earlier pilot was largely null [212]. Hyaluronic acid gave  $-3.3 \pm 0.3$  cm versus  $-2.4 \pm 0.3$  ( $p = 0.029$ ) in 168 patients [213]. Bone-marrow aspirate concentrate evidence is a 19-patient uncontrolled series [214] and adipose-derived evidence a 14-patient crossover [215]. The amnion–chorion trial is, on the evidence retrieved, the only adequately powered placebo-controlled randomised trial of an orthobiologic in a fascial disease.

Surgical and procedural. For Dupuytren contracture, a GRADE assessment rated high to moderate

concluded that percutaneous needle fasciotomy, collagenase and limited fasciectomy are equally effective long term, with limited fasciectomy showing the lowest recurrence and the evidence favouring needle fasciotomy over collagenase [216]. The 672-patient DISC trial across 31 hospitals found differences of 5.95 (3.12–8.77) at one year and 7.18 (4.18–10.88) at two years, providing little evidence to reject the inferiority of collagenase, which was cheaper by £1090 but delivered 0.048 fewer quality-adjusted life years [217]. Regulatory status must be read separately from efficacy: collagenase remains approved in the United States at 0.58 mg per cord with a tendon-rupture rate of 3 in 1082 [218], while the European authorisation was withdrawn effective 1 March 2020 and the Canadian authorisation cancelled on 15 June 2020, both for commercial rather than safety reasons [219]. Focused shockwave devices hold premarket approvals P000048 and P040026, the former withdrawn in 2018 without stated reason [221], and percutaneous tenotomy is cleared under K181367 [223]. Endoscopic and open plantar fasciotomy produce no outcome difference, but endoscopic surgery is shorter (15.76 versus 36.78 minutes) with fewer complications (5% versus 11%) [224], and fascia-preserving gastrocnemius recession gives a standardised mean difference of 0.81 [225].

### Methodological quality of the review base

The most important single number in the therapeutic literature is not an effect size. Across 96 systematic reviews of myofascial interventions, AMSTAR-2 confidence was critically low in 75% and high in only 4.2% [14]. This is the context in which every pooled estimate above should be read: the field is review-rich and certainty-poor. Four further records that are commonly cited as review-level evidence are, on inspection, a Cochrane protocol without results [226] or reviews without a reproducible systematic search [227–229], and we flag them as non-systematic rather than counting them.

| Cell type                   | Defining markers or morphology                                                        | Reported quantity                                                  | Source  |
|-----------------------------|---------------------------------------------------------------------------------------|--------------------------------------------------------------------|---------|
| Fasciocyte                  | HAS2+, S100A4+, vimentin+, CD68–; Alcian blue and HABP positive                       | ~30% of fibroblast-like cells of deep fascia                       | [2,28]  |
| Telocyte                    | Cell body $9.39 \pm 3.26 \mu\text{m}$ , telopodes up to $\sim 22 \mu\text{m}$ ; CD34+ | 0–2 per field of view in fascia lata                               | [29]    |
| Mast cell                   | Metachromatic granules; perineural clustering                                         | $20.4 \pm 9.4/\text{mm}^2$ in superficial fascia; ~25% near nerves | [34]    |
| Myofibroblast               | $\alpha\text{-SMA}+$                                                                  | Median 1.52% lumbar fascia; 0% plantar fascia and fascia lata      | [35]    |
| CD201+ fascia progenitor    | CD201+, multipotent                                                                   | Not quantified as a tissue fraction                                | [5,16]  |
| Fibro-adipogenic progenitor | PDGFR $\alpha$ +, Sca1+; Hic1, Tie2/Vcam1 subsets                                     | Not quantified in human fascia                                     | [7,55]  |
| Macrophage (disease)        | CD68/myeloid clusters; SPP1+ subset                                                   | $11.2 \pm 6.6\%$ in gluteal contracture vs $1.8 \pm 1.0\%$ control | [39,41] |

**Table 1:** Fascial cell populations and their quantitative characterisation.

| Parameter                                    | Value                                                                           | Source |
|----------------------------------------------|---------------------------------------------------------------------------------|--------|
| Deep fascia overall thickness                | $\sim 1 \text{ mm}$ , 2–3 collagen sublayers                                    | [1]    |
| Crural fascia total thickness                | $924 \mu\text{m}$ ; sublayers $277.6 \mu\text{m}$ ; interlayer $43 \mu\text{m}$ | [22]   |
| Fascia lata thickness                        | $926 \pm 156 \mu\text{m}$                                                       | [2]    |
| Thoracolumbar fascia, chronic LBP vs control | $2.11 \pm 0.65$ vs $1.75 \pm 0.85 \text{ mm}$                                   | [135]  |

| Parameter                                       | Value                                                  | Source |
|-------------------------------------------------|--------------------------------------------------------|--------|
| Plantar fascia, fasciitis vs control            | 6.07 ± 2.37 vs 3.28 ± 0.41 mm; 4 mm cutoff<br>AUC 0.97 | [167]  |
| Elastic fibre content                           | ~15% epimysial vs <1% aponeurotic fascia               | [2]    |
| Hyaluronan, ankle retinacula                    | ~90 µg/g                                               | [86]   |
| Hyaluronan, fascia lata / rectus sheath         | ~35 / ~29 µg/g                                         | [86]   |
| Hyaluronan, trapezius and deltoid fascia        | ~6 µg/g                                                | [86]   |
| Nerve fibre density, TLF vs latissimus dorsi    | 3.4 ± 0.6 vs 1.0 ± 0.1 per 40,000 µm <sup>2</sup>      | [3]    |
| Sympathetic share of fascial innervation        | ~40%                                                   | [2,38] |
| Aging: lower-limb vs low-back fascial thickness | -12.3 to -25.8% vs +40.0 to +76.7%                     | [25]   |

**Table 2:** Quantitative morphology and matrix chemistry of human fascia.

| Intervention                                 | Best available pooled estimate                                     | Reported certainty                   | Source    |
|----------------------------------------------|--------------------------------------------------------------------|--------------------------------------|-----------|
| Myofascial release, chronic LBP              | Disability SMD -0.35 (-0.68, -0.02); pain NS                       | Moderate (GRADE)                     | [172]     |
| Massage, myotendinous stiffness              | SMD -0.17 (NS)                                                     | Not stated                           | [175]     |
| Instrument-assisted mobilisation             | Pain SMD 0.60; function SMD -0.28 (NS)                             | Moderate vs very low (conflicting)   | [10,177]  |
| Foam rolling                                 | ROM ES 0.823; no performance or stiffness change                   | Not stated                           | [178,180] |
| Dry needling                                 | Short-term SMD -1.91; no advantage over modalities                 | High risk of bias in all 8 RCTs      | [9,184]   |
| 5% dextrose hydrodissection                  | Superior to saline MD -1.30; best SUCRA rank                       | Low                                  | [187]     |
| Extracorporeal shockwave                     | SMD -0.60; only modality effective medium and long term (MD -2.49) | Low to very low                      | [191,194] |
| Photobiomodulation                           | MD -22.02 vs control; -20.94 vs shockwave                          | Not stated                           | [195]     |
| Therapeutic ultrasound                       | No benefit                                                         | Low                                  | [197]     |
| Corticosteroid injection, plantar heel       | MD -6.38 (-11.13, -1.64) against MID of 8                          | Low                                  | [199]     |
| Botulinum toxin, neck/shoulder               | MD -10.22 (0-100); not recommendable                               | Low                                  | [203]     |
| Prolotherapy                                 | WMD -41.72 vs saline                                               | Low                                  | [204]     |
| Platelet-rich plasma                         | Superior to corticosteroid 3-12 months; no thickness change        | 9/15 RCTs high risk of bias          | [207]     |
| Amnion-chorion membrane                      | VAS -76% vs -45% (p < 0.0001); FFI-R -60% vs -40%                  | Adequately powered multicentre RCT   | [211]     |
| Cupping                                      | Uncertain benefit                                                  | Very low; 4/5 RCTs high risk of bias | [198]     |
| Dupuytren: PNF vs collagenase vs fasciectomy | Equally effective long term; LF lowest recurrence                  | High to moderate (GRADE)             | [216]     |

**Table 3:** Review-level evidence for fascia-directed interventions, with reported certainty.

## Discussion

### A single mechanism, many diseases

The most defensible synthesis this literature supports is that fascial disorders are the pathological settings of one conserved mechanochemical axis. Stretch and stiffness are read by integrins and Piezo1, transduced through Rho-kinase and YAP/TAZ, and executed by transforming growth factor beta-1 that is liberated mechanically from the matrix it is stored in [109,111-113]. Fascia participates in this axis directly rather than by analogy, since shockwave, angiotensin II and androgen all modulate YAP or collagen composition in human fascial tissue and cells [114,117]. Around that core, the hyaluronan layer supplies a fast, reversible, rheological control loop with third-to-fourth-power sensitivity to concentration, and the

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fasciocyte is its dedicated effector cell [28,91].

That framing accounts for why immobility converts a reversible hyaluronan state into irreversible collagenous thickening [88], why stretch is anti-inflammatory through resolvin D1 rather than mechanical rearrangement alone [123], why needling produces dose-dependent, non-monotonic cytoskeletal responses [118], and why aging moves fascia in opposite directions in different regions according to local loading history [25].

### **Why the biology has not yet reached patients**

The gap between this biology and clinical practice is not a translational lag; it is a series of specific, nameable absences. There is no first-in-human trial of any fascia-derived cellular product and no trial of mesenchymal stromal cells or stromal vascular fraction injected into any fascia. There is no fascia-specific extracellular-vesicle study, no bioprinted fascial construct, and no in vitro study of platelet-rich plasma applied to fascial fibroblasts, despite platelet-rich plasma being among the most frequently injected agents into fascial tissue [75,207]. There is no biglycan- and fibromodulin-defined progenitor niche described for fascia comparable to the one established for tendon [230], and no progenitor-level study of plantar fibromatosis.

Three further absences constrain interpretation of everything that does exist. First, no healthy human deep-fascia single-cell atlas has been published; both existing datasets are surgical disease [40]. Second, the identity relationship between telocytes and fibro-adipogenic progenitors is unresolved [31]. Third, matrix metalloproteinase, tissue inhibitor and lysyl oxidase quantification in human deep fascia is simply missing, so the crosslinking narrative in fascia is imported wholesale from tendon, lung and tumour stroma [231].

### **The measurement problem is upstream of the treatment problem**

The therapeutic tables above should be read not as a modality ranking but as a statement about measurement. When the index diagnosis is applied with an interrater kappa of 0.452 [125], when elastographic values are not transferable between devices [165], when the most-cited mechanical marker of fascial dysfunction points in opposite directions in two well-conducted studies [136], and when three quarters of relevant systematic reviews are of critically low AMSTAR-2 confidence [14], the ceiling on demonstrable treatment effect is set before any intervention is chosen.

The quantitative-ultrasound trial that dissociated mechanical change from clinical change makes this concrete: manual therapy demonstrably altered thoracolumbar fascia shear strain, and that alteration did not track disability [176]. Similarly, platelet-rich plasma improved pain without altering fascial thickness [208]. Mechanistic surrogates in fascia are, so far, not validated as outcome surrogates, and should not be used as primary endpoints until they are.

### **What is genuinely established**

Five claims survive scrutiny: fascia contains a dedicated hyaluronan-producing cell type with a defined marker profile [28]; it is more densely innervated than the muscle it invests and more painful under experimental chemical stimulation [3]; it contains a multipotent progenitor that supplies both cells and

pre-assembled matrix to scar [5]; fascial thickening is a replicable imaging finding in chronic low back pain and plantar fasciopathy [133,142]; and fascial fibrosis, in the two human diseases sequenced so far, is macrophage-associated rather than myofibroblast-dominated [41].

Five widely repeated claims do not survive. Fascia is not uniformly proprioceptive, since corpuscular receptors are absent from thoracolumbar fascia and fascia lata [2,38]; the superficial front line has no verified anatomical transitions [106]; densification has no direct human histological confirmation [88]; reduced fascial shear strain in low back pain does not replicate [137]; and fascia is not generally contractile, myofibroblasts being absent from plantar fascia and fascia lata [35].

### **A research agenda**

Four priorities follow. First, a healthy-donor single-cell and spatial atlas of human muscular fascia, without which no disease dataset can be properly normalised. Second, a validated case definition for myofascial pain with interrater reliability meaningfully above 0.45, since no trial programme can outperform its own diagnostic ceiling. Third, a phase I trial of an autologous fascia-derived cellular product, which the *in vitro* and animal evidence now amply justifies [73,75]. Fourth, head-to-head comparison of the two interventions with the most credible existing data — extracorporeal shockwave, the only modality effective at medium and long term in the largest network [194], and amnion–chorion membrane, the only orthobiologic with an adequately powered placebo-controlled trial [211] — using endpoints anchored to condition-specific minimal important differences [170].

### **Limitations**

Four limitations should be weighed. The design is hybrid, and the narrative strand covering cell and progenitor biology was not conducted as a systematic review, because that literature presently has too few comparable studies to pool. The umbrella strand inherits the quality of its constituent reviews, which is predominantly critically low by their own AMSTAR-2 assessment [14]. Definitional heterogeneity across three coexisting nomenclatures means some pooling in the source reviews may combine non-equivalent tissues. Finally, the searches were not registered in advance, so this work should be read as a comprehensive critical synthesis rather than a protocol-registered systematic review.

### **Conclusion**

Muscular fascia is best understood not as packing tissue and not as a mystical continuum, but as a mechanically gated progenitor and immune compartment with its own resident cell types, a site-specific matrix chemistry tuned to local sliding demand, an innervation denser than that of the muscle it invests, and a conserved mechanotransduction axis that its diseases dysregulate. The biological case for fascia as a regenerative target is now strong, resting on a defined fascial progenitor, an indispensable fibro-adipogenic progenitor population, and fascia-derived cells that outperform adipose-derived cells in comparative assays. The clinical case is far weaker, and for identifiable reasons: no fascia-derived cellular product has entered a human trial, no healthy human fascial single-cell reference exists, the dominant clinical diagnosis has poor interrater reliability, mechanical surrogates have not been validated as outcome surrogates, and three quarters of the relevant systematic reviews are of critically low confidence. The field's next decade will be decided less by new modalities than by whether it can define its diagnoses

reproducibly and test its most promising biology in patients.

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## Conflict of interest

The author declares no conflict of interest.

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## Ethics statement

This study is a review of previously published literature and involved no human participants, identifiable human data or animal experimentation. It therefore did not require approval by a research ethics committee or institutional review board.

## Use of artificial intelligence

Artificial-intelligence tools were used to assist with literature retrieval, reference formatting and language editing. All scientific content, interpretation and verification of quantitative values against source records are the responsibility of the author.

## Data availability

All data discussed in this review are contained within the cited published sources.

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