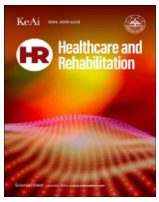
Healthcare and Rehabilitation 2 (2026) 100094

Contents lists available at ScienceDirect

Healthcare and Rehabilitation

journal homepage: www.keaipublishing.com/en/journals/hcr/



Perspective

Macro to micro: A perspective on cell-directed physical therapy for next-generation rehabilitation

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ARTICLE INFO

Keywords:
Rehabilitation therapy
Cellular functions
Physical stimuli
Micro-rehabilitation
Biophysical regulation

1. Introduction

A paradigmatic case is that of a stroke survivor whose ambulatory capacity remains suboptimal despite intensive gait rehabilitation; this discrepancy is largely attributable to post-stroke muscle fibrosis and consequent extracellular matrix (ECM) stiffening. An equivalent situation arises in a patient who, despite anatomically satisfactory prosthetic alignment following knee arthroplasty, endures chronic pain driven by persistent synovial inflammation or peripheral/central sensitization. These clinical presentations illustrate a central therapeutic dilemma: deficits manifesting at the macroscopic functional level are frequently rooted in occult persistent cellular pathologies that evade current interventions. In the stroke population, fibrosis-induced increases in ECM stiffness not only mechanically impede sarcomere shortening and force transmission but also sustain aberrant proprioceptive afferent signals, thereby attenuating activity-dependent cortical reorganization. Conversely, in the arthroplasty cohort, dysregulated chondrocyte metabolism fuels low-grade intra-articular inflammation and intensifies nociceptor sensitivity, such that persistent pain effectively overwhelms any motor gains achieved through conventional gait training. Therefore, although traditional rehabilitation paradigms—whether neurodevelopmental, constraint-induced, or robot-assisted—undisputedly promote functional restitution via plasticity induced by repetitive behavioral experience, they are constrained by two interdependent limitations. The first is indirectness: cellular pathophysiology is addressed only indirectly through systemic or neural modulation rather than via targeted molecular correction. The second is unidimensionality: the therapeutic lens remains narrowly focused on neural circuitry and muscular performance, to the near-exclusion of the ECM microenvironment, mitochondrial bioenergetic status, and the inflammatory-fibrotic crosstalk that perpetuates tissue dysfunction. These omissions may, in part, explain the frequently observed ceiling effects, even in optimally delivered rehabilitation programs.

Over the preceding decade, synergistic advancements in biomechanics and biophysics have fundamentally revised this view: far from functioning solely as biochemical reaction vessels, cells operate as exquisitely sensitive physical signal transducers. Evidence demonstrates that cells continuously monitor and adapt to matrix stiffness via integrin-mediated mechanotransduction cascades that converge on transcriptional programs governing lineage specification, thereby critically determining the balance between homeostatic differentiation and pathological fibrosis.[1] Exposure to specific electromagnetic fields

Abbreviations: ATP, adenosine triphosphate; ECM, extracellular matrix; SCI, spinal cord injury; 3D, three-dimensional; LIFU, low-intensity focused ultrasound; YAP, Yes-associated protein

Peer review under responsibility of Shandong University.

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https://doi.org/10.1016/j.hcr.2026.100094
Received 4 June 2026; Received in revised form 26 August 2026; Accepted 27 August 2026
Available online 7 September 2026
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dynamically modulates oscillatory calcium activity, thereby affecting stem cell commitment trajectories.[2] Similarly, pulsed ultrasound has emerged as a noninvasive modality capable of enhancing neuronal survival and neurotrophic factor expression *in situ*.[3] These mechanistic insights have propelled the rational design of integrated therapeutic platforms. In these platforms, physical agents, including photonic, mechanical, electrical, magnetic, and acoustic modalities,[4,5] are coupled with biomaterial scaffolds to function as precision effectors targeting distinct cellular functional modules to orchestrate tissue repair and regenerative responses. Synthesizing these convergent findings, we propose a conceptual shift: to reconfigure the therapeutic unit of rehabilitative intervention, shifting the level of analysis from macroscopic joint or limb structures to discrete, pathologically relevant cellular functional modules; and to support the deliberate, algorithm-guided application of exogenous physical stimuli to achieve fine-grained, micro-scale regulatory control over these modules.

2. Traditional rehabilitation and micro-rehabilitation therapy

2.1. Current rehabilitation landscape

A growing body of clinical evidence supports the efficacy of physical rehabilitation modalities such as low-intensity focused ultrasound (LIFU), microcurrent electrical stimulation, and pulsed electromagnetic fields, across a range of indications, including pain modulation, postural control, and motor restoration. In a representative randomized controlled trial, patients with myofascial pain syndrome of the upper trapezius showed significant improvements in pain perception and functional disability scores after treatment with LIFU at 1.5 W/cm^2, 1 MHz, for 5 min daily over 3 days.[6] Similarly, a separate randomized controlled trial in chronic stroke survivors reported that adjunctive microcurrent stimulation delivered to the gastrocnemius over 8 weeks significantly enhanced plantar pressure symmetry and dynamic balance, outperforming a conventional rehabilitation protocol.[7] Nevertheless, these promising outcomes should be interpreted with caution, as the cellular and molecular underpinnings of such physical interventions remain epiphenomenally observed, but are not prospectively engineered in most instances (Table 1). Compounding this issue, most preclinical rehabilitation studies continue to prioritize behavioral recovery as the terminal endpoint while systematically neglecting to validate the impact of physical stimuli on discrete cell populations or pathological cellular states. This confluence of translational gaps leads to a persistent and clinically consequential dilemma: effective interventions cannot be rationally optimized because their mechanisms are opaque, whereas ineffective interventions cannot be salvaged, as the determinants of failure remain unidentified. Breaking this impasse demands a paradigmatic reorientation that positions the cell as a targetable, programmable physical–biological interface whose responses to exogenous physical cues can be characterized, predicted, and ultimately harnessed.

2.2. Prospects of micro-rehabilitation therapy

In physiological tissues, cells are embedded within and engage in continuous reciprocal crosstalk with the ECM, a structurally dynamic three-dimensional (3D) composite of fibrous proteins, glycoproteins, and proteoglycans. Although the ECM has long been acknowledged for its mechanical scaffolding properties, accumulating evidence has established that it concurrently serves as a conduit for a substantially diverse repertoire of physical signals, encompassing mechanical forces,[13] bioelectric fields,[14] and photonic energy,[15] each capable of modulating cellular states and functional outputs (Table 2). These observations collectively affirm the conceptual tenet that cells are not merely biochemical reaction vessels, but rather function as sophisticated, context-sensitive physical signal transducers. For example, the Hippo/Yes-associated protein (YAP) axis is a mechanotransductive node through which physical interventions (e.g., therapeutic exercise, ultrasound, vibration, and manual therapy) convert mechanical cues into transcriptional responses that regulate proliferation, lineage specification, and repair.[16] This mechanistic paradigm provides a coherent molecular rationale that directly links physical therapeutic input to the rectification of pathological cellular phenotypes. Grounded in this conceptual foundation, we formally introduce the term micro-rehabilitation therapy (Fig. 1), which we define as a class of targeted interventions that act directly on cellular functional modules (such as ion channels, cytoskeleton, organelles, and nuclear mechanotransducers) through either deliberate exogenous application of physical stimuli (optical, mechanical, electrical, magnetic, or acoustic modalities[2,3]) or sustained, localized delivery through implantable platforms (e.g., stimuli-responsive biomaterials[4,5]). The therapeutic objective is clear: to reverse maladaptive cellular phenotypes at their source with the aim that such molecular-scale corrections will propagate upward to yield measurable macroscopic improvements in function or tissue integrity. At this juncture, micro-rehabilitation therapy must be distinguished from the adjacent yet conceptually distinct domain of regenerative rehabilitation. Conventionally, regenerative rehabilitation involves the integration of regenerative medicine modalities (e.g., stem cell-based therapies, tissue engineering, biomaterials, and gene editing) and rehabilitation sciences to enhance functional outcomes by promoting tissue regeneration.[17] Its foundational logic is based on a substitutional approach: the introduction of exogenous cells, matrices, or molecular cues to replace damaged or missing tissue components, with rehabilitation playing a supporting role in promoting engraftment, modulating differentiation, and enabling functional assimilation.[18] By contrast, micro-rehabilitation therapy adheres to a fundamentally different therapeutic logic that is corrective rather than substitutive. It operates entirely within the host tissue environment, targeting pre-existing functionally aberrant cellular modules and rectifying their pathological states through precision-engineered physical interventions. In short, whereas regenerative rehabilitation poses the question "*How can rehabilitation serve regeneration*?", micro-rehabilitation therapy advances a distinct and more radical query: "*How can rehabilitation itself be configured to directly normalize pathological cellular states in their native context*?"

The management of spasticity following spinal cord injury (SCI) is an instructive paradigm. Conventional rehabilitative interventions, including passive mobilization, sustained stretching, manual massage, functional electrical stimulation, and thermal or cryotherapeutic applications, can ameliorate symptomatic manifestations; however, they exert no direct influence on the neural and glial pathomechanisms that underpin and perpetuate the spastic phenotype. To address this fundamental limitation, we propose a proof-of-concept micro-

Table 1
Cellular-level effects of conventional rehabilitation interventions.

Intervention	Primary goal	Passive cellular-level effects
Exercise training	Improve strength and coordination of limbs	Mitochondrial biogenesis, angiogenesis[8,9]
Transcutaneous electrical stimulation	Pain relief, neural activation	Altered membrane potential of peripheral nerves[10]
Thermotherapy/cryotherapy	Reduce oedema, relieve pain	Inflammatory responses and local cellular metabolic rate[11]
Manual stretching	Increase range of motion	May transiently activate mechanosensitive channels[12]

Table 2
Representative physical factors and rehabilitation-relevant effects.

Physical factor	Putative cellular targets	Rehabilitation-relevant biological effect	Representative applicable diseases
Light	Optogenetic proteins, cytochrome c oxidase, mitochondrial respiratory chain	Suppress pain circuits, increase ATP synthesis, inflammatory regulation	Musculoskeletal pain, wound healing, neuropathic pain, osteoarthritis
Force/ultrasound	Integrins, focal adhesions, Piezo1/2 channels, primary cilia	Reverse matrix stiffening feedback, induce fibroblast deactivation	Tendinitis, bursitis, contractures, osteoarthritis, bone injuries
Electric field	Membrane potential, voltage-gated ion channels	Guide cell migration (galvanotaxis), steer stem cell differentiation	Chronic pain, muscle re-education, wound healing
Magnetic field	Magnetogenetic proteins, radical-pair mechanisms, certain ion channels	Remote, non-invasive control of deep tissues, modulate neural firing rhythms	Bone healing, osteoarthritis, nerve regeneration

Abbreviation: ATP, adenosine triphosphate

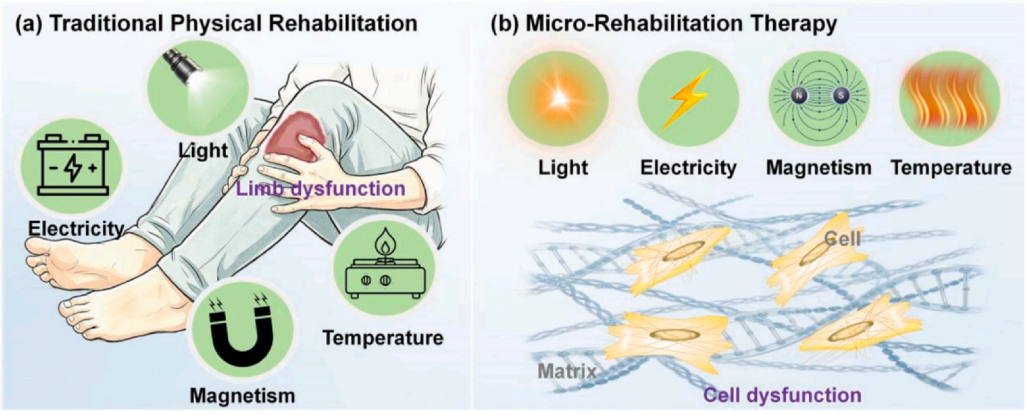


Fig. 1. Comparison diagram of traditional rehabilitation and micro-rehabilitation therapy.

rehabilitation framework that explicitly targets cellular- and circuit-level drivers. The initial procedural step entails the precise identification of the pathological substrate. Recent implementations show that ultraflexible electrodes enable stable, single-unit neuronal recordings from the spinal cords of freely moving mice, overcoming motion-induced noise that previously compromised the fidelity of conventional microwire recording.[19] Therefore, piezoresistive microneedle arrays fabricated from ultra-flexible polymers offer a technologically advanced approach to achieving this objective. This neuromapping strategy has the potential to localize spinal motor neuron pools that exhibit pathologically elevated firing frequencies within the spastic muscle territories. Nevertheless, the clinical translation of this technology is confronted with substantial challenges: the degree of insertion-related tissue trauma remains non-negligible relative to that of microwire comparators, and the sustained biocompatibility of polymer interfaces in the human spinal intrathecal space remains unclear. A subsequent therapeutic maneuver, predicated on the successful mapping of hyperactive motor neuron pools, involves delivering targeted magnetic stimulation at specified frequencies, thereby attenuating pathological neuronal firing. Repetitive peripheral magnetic stimulation has shown preliminary efficacy in mitigating post-stroke spasticity.[20] However, the optimization of its frequency parameters and the relative contributions of its biomechanical and neurophysiological mechanisms remain debatable. Furthermore, its applicability to SCI-specific spasticity has not been evaluated in a dedicated, adequately powered clinical study. In parallel, to target the glial component of spasticity pathogenesis, LIFU may be applied to suppress the activity of reactive astrocytes within the spinal cord tissue that produce pro-spastic molecular mediators. This interventional choice is supported by experimental evidence demonstrating that LIFU confers non-invasive spinal neuromodulation by reprogramming reactive astrocytes and providing sustained neuropathic pain relief.[21] The intended clinical endpoint is spasticity reduction without concomitant compromise of voluntary motor capacity, thereby avoiding muscle atrophy frequently associated with prolonged immobilization or chronic pharmacological suppression. Moreover, functional recovery following neurological injury should not be recognized as a unitary process, but rather as a series of temporally segregated phases: acute (minutes to days), subacute (days to weeks), and chronic (weeks to months), each distinguished by a characteristic pathophysiological profile, a distinct hierarchy of therapeutic priorities, and a differential sensitivity to rehabilitative training. For example, in the context of ischemic stroke, neuroprotection dominates the acute phase, functional rehabilitation becomes primary in the subacute and chronic phases, and spontaneous neuroplasticity peaks at approximately 3–4 weeks.[22] Therefore, intervention strategies must be tailored to the prevailing phase. Accordingly, we propose a tiered, phase-dependent integration strategy for micro-rehabilitation. During the acute phase (0–7 days), micro-rehabilitation warrants cautious application, as intensive activity within the initial 24 h carries a potential risk of exacerbating the injury. The clinical imperative is instead neuroprotection and mitigation of secondary pathological cascades.[22] The subacute phase (1 week to 6 months) represents a critical “therapeutic window of opportunity”, characterized by a permissive inflammatory environment and amplified neuroplastic capacity.[23] During this interval, micro-rehabilitation should be actively integrated, such as employing LIFU to modulate cortical excitability, microcurrent stimulation to reinforce muscle activation and proprioceptive reafference, and pulsed electromagnetic fields to sustain mitochondrial bioenergetic homeostasis in metabolically compromised tissue. In the chronic phase ($>$ 6 months), overall responsiveness to intervention diminishes but does not disappear completely. Micro-rehabilitation should strategically pivot toward the targeted amelioration of persistent cellular pathologies, including reversal of fibrotic deposition, modulation of cytoskeletal organization, and reprogramming of metabolic dysregulation, to overcome the functional plateau that typically delimits the efficacy of conventional therapeutic regimens. Collectively, these examples demonstrate that micro-rehabilitation is not intended to supplement existing therapeutic modalities. Rather, it constitutes a complementary,

mechanism-anchored precision approach that directly addresses cellular- and circuit-level pathophysiologies that remain largely unaddressed by conventional rehabilitation paradigms.

3. Translational challenges and future directions

A salient challenge confronting the proposed conceptual framework pertains to its apparent generalizability across a heterogeneous array of pathological conditions ranging from focal neurological injuries to degenerative musculoskeletal disorders and progressive neurodegenerative diseases. We contend that this apparent breadth is not fortuitous, but rather derives from a mechanistic convergence at the level of fundamental cellular functional modules, which exhibit intrinsic physical responsiveness largely independent of tissue provenance. This shared mechanistic basis provides the conceptual foundation upon which micro-rehabilitation therapy is based. However, conceptual unity does not equate to operational uniformity. Specific physical parameters such as frequency, intensity, duty cycle, and modality, along with delivery routes and targeted cellular substrates, must be meticulously calibrated to each disease context, given that the predominant pathogenic drivers are not only disparate but often disease-specific. Thus, rather than offering a singular translational roadmap, our framework posits a generalizable investigative logic in which condition-specific mechanistic hypotheses and intervention protocols are iteratively refined through systematic, disease-focused empirical inquiry.

Notably, the rehabilitation modalities discussed herein are not clinically interchangeable. They span a considerable gradient of technological maturity, from well-established modalities with regulatory antecedents (e.g., therapeutic ultrasound and peripheral electromagnetic stimulation) to nascent experimental platforms that remain predominantly within the preclinical arena (e.g., optogenetics and implantable bioresponsive materials). Thus, the translational trajectory of micro-rehabilitation therapy from laboratory to clinic faces substantial challenges. First, persistent technical impediments to targeted delivery constrain current capabilities, and the evidentiary basis remains preclinical. Although LIFU and pulsed electromagnetic fields have demonstrated therapeutic efficacy in selected clinical contexts, the body of rigorous, adequately powered, multicenter randomized controlled trials conducted specifically within rehabilitation populations is limited. Furthermore, physical modalities differ intrinsically in their tissue penetration profiles and are not inherently innocuous. Their application entails potential risks that must be systematically characterized. This inherent gap underscores the urgent need for the establishment of standardized stimulation protocols, the validation of mechanism-anchored biomarkers, and the design of pragmatic clinical trials. Second, interindividual heterogeneity complicates the application and generalizability of micro-rehabilitation principles. Responsiveness to a given physical modality exhibits marked variability across patients. Within the micro-rehabilitation paradigm, such variability may arise from disparate sources, including differences in tissue composition, lesion localization, and individual mechanosensitivity thresholds. Therefore, future research should prioritize robust patient stratification strategies and, where methodologically feasible, incorporate model-based optimization approaches to enable the personalization of stimulation parameters informed by individual-specific anatomical and pathological characteristics. Third, technical and regulatory challenges remain substantial. These include the miniaturization of devices to enable concurrent use with limb training protocols, acoustic interference and attenuation caused by bony structures when targeting deep spinal targets, the long-term biocompatibility and stability of epidermal or implantable interfaces, and the substantial financial and regulatory burdens associated with device development and market authorization processes. We identify three priority directions to advance the field: (a) the conduct of large-scale pragmatic trials comparing micro-rehabilitation interventions with standard care, incorporating conventional functional assessments and mechanistic cellular-level endpoints; (b) the development of closed-loop adaptive systems capable of real-time titration of physical factor delivery in response to cellular or physiological readouts; and (c) the fostering of interdisciplinary collaborations across engineering, materials science, neuroscience, and clinical rehabilitation to co-design solutions that are not only conceptually innovative but also clinically translatable.

4. Conclusions

In contrast to conventional rehabilitation, which predominantly operates at the macroscopic level of limbs and neural circuits, eliciting cellular effects indirectly and as secondary consequences, micro-rehabilitation therapy is founded on the active, direct, and deliberate modulation of cellular phenotypes. It is not proposed as a substitute for established rehabilitative modalities but rather as a powerful and complementary approach that directly confronts the cellular pathomechanisms that remain inaccessible to limb-based interventions. We revisit the clinical scenarios that framed this perspective: the patient with stroke who fails to achieve functional ambulation despite intensive gait training, and the knee arthroplasty recipient who continues to experience debilitating pain despite well-aligned prosthetic components. In this context, micro-rehabilitation would directly target fibrotic myofibroblasts and matrix-stiffening mechanotransductive pathways using LIFU or focused magnetic stimulation, thereby disrupting the vicious, self-reinforcing cycle of pathological ECM remodeling, which renders passive stretch-based therapies largely ineffective. Simultaneously, pulsed electromagnetic fields or photobiomodulation could be deployed to stabilize metabolically dysregulated chondrocytes and attenuate nociceptive sensitization at its peripheral source, thereby addressing the cellular determinants of pain that joint alignment alone cannot resolve. Accordingly, by delivering precisely engineered physical stimuli directly to the cellular level, micro-rehabilitation offers a generalizable heuristic for overcoming functional ceilings that pervasively delimit the efficacy of conventional rehabilitative paradigms. The ultimate translational impact of this framework across disparate pathological entities will depend on rigorous, disease-specific validation of target relevance, systematic parameter optimization, and stepwise functional translation through a carefully staged empirical investigation. However, while mechanistically grounded and supported by an expanding body of preclinical evidence, this conceptual framework has not yet been clinically validated. A substantial translational agenda remains to be accomplished before micro-rehabilitation can be incorporated into routine clinical practice. Nevertheless, the underlying principles are sufficiently compelling to justify sustained and systematic investigations. We believe that this perspective has the potential to facilitate interdisciplinary collaborative efforts to translate these concepts into demonstrable patient benefits.

Ethics approval

Not applicable.

Funding information

This work was financially supported by the Shandong Province Traditional Chinese Medicine Science and Technology Project (Grant No. M20254801), Talent Development Plan for the Future in Medical-Engineering Integration by BRA-CDCHE and ZT (Grant No. MBRC0012025017), Chronic Disease Management Research Project of National Health Commission Capacity Building and Continuing Education Center (Grant No. GWJJMB202510021102), Shandong Province Medical and Health Science and Technology Project (Grant No. 202525020643), and Special Program for Enhancing Clinical Research Capabilities of UHRS (Grant No. K2025LC7305).

CRediT authorship contribution statement

Xiaojuan Li: Writing – original draft, Writing – review & editing. **Wufei Dai:** Writing – review & editing. **Bingcheng Yi:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. All the authors have read and approved the final version of this manuscript.

Data availability

Not applicable.

Declaration of Competing Interest

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

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that no generative AI or AI-assisted technologies were used in the writing process.

Acknowledgments

None.

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