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Mechanome-guided strategies in regenerative rehabilitation

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Abstract

Regenerative Rehabilitation represents a multifaceted approach that merges mechanobiology with therapeutic intervention to harness the body's intrinsic tissue repair and regeneration capacity. This review delves into the intricate interplay between mechanical loading and cellular responses in the context of musculoskeletal tissue healing. It emphasizes the importance of understanding the phases involved in translating mechanical forces into biochemical responses at the cellular level. The review paper also covers the mechanosensitivity of macrophages, fibroblasts, and mesenchymal stem cells, which play a crucial role during regenerative rehabilitation since these cells exhibit unique mechanoresponsiveness during different stages of the tissue healing process. Understanding how mechanical loading amplitude and frequency applied during regenerative rehabilitation influences macrophage polarization, fibroblast-to-myofibroblast transition (FMT), and mesenchymal stem cell differentiation is crucial for developing effective therapies for musculoskeletal tissues. In conclusion, this review underscores the significance of mechanome-guided strategies in regenerative rehabilitation. By exploring the mechanosensitivity of different cell types and their responses to mechanical loading, this field offers promising avenues for accelerating tissue healing and functional recovery, ultimately enhancing the quality of life for individuals with musculoskeletal injuries and degenerative diseases.

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From mechanotherapy to regenerative rehabilitation

Without any exception, all musculoskeletal tissue (MSK) tissues, including bone, tendon, ligament, intervertebral discs, cartilage, etc., are under constant mechanical loading due to diurnal and recreational activities [1]. The mechanical loading applied on MSK tissues is crucial to keep the MSK in a hemostasis state, so many prominent studies have been conducted to understand the intertwined relationship between mechanical forces and cellular responses [2]. These studies demonstrated that direct physical stimuli applied to tissues incite biological processes at the cellular level through cellular mechanotransduction at the interface between the extracellular matrix (ECM) and the cell membrane [3]. In fact, the ancient Chinese, Greek, Roman, and Egyptian civilizations used this concept, applied mechanical loading for MSK tissue healing, and established the roots of mechanotherapy [4,5]. Mechanotherapy, an emergent concept bridging mechanobiology and therapeutic intervention, uses mechanical forces to alter molecular pathways and evoke cellular responses conducive to tissue growth, remodeling, and repair [5]. This multifaceted strategy aims to restore and establish normal tissue functions following loss due to injury, aging, and exposure to microgravity through employing mechanotherapeutic approaches. However, many musculoskeletal tissues are inherently limited in spontaneously regenerating and repairing following injuries, even with the help of mechanotherapy. Thus, the cells, biologics, and carrying platforms, including extracellular vesicles (EVs) from stem cells, fibroblasts, and cellular scaffolds as regenerative agents, have been utilized along with mechanotherapy to improve tissue healing [4,6–8]. This paved the way for establishing the field of regenerative rehabilitation, which integrates principles from regenerative medicine (stem cells, extracellular vesicles, scaffolds, etc.) with mechanotherapy for enhanced tissue regeneration and functional tissue recovery.

Understanding the regenerative rehabilitation strategies at the cellular level

Regenerative rehabilitation is a multidisciplinary field bringing rehabilitation specialists, occupational therapists, basic scientists, tissue engineers, and surgeons together to be used in a wide range of conditions, including musculoskeletal injuries (such as fractures, tendon, and ligament tears), neurological disorders (such

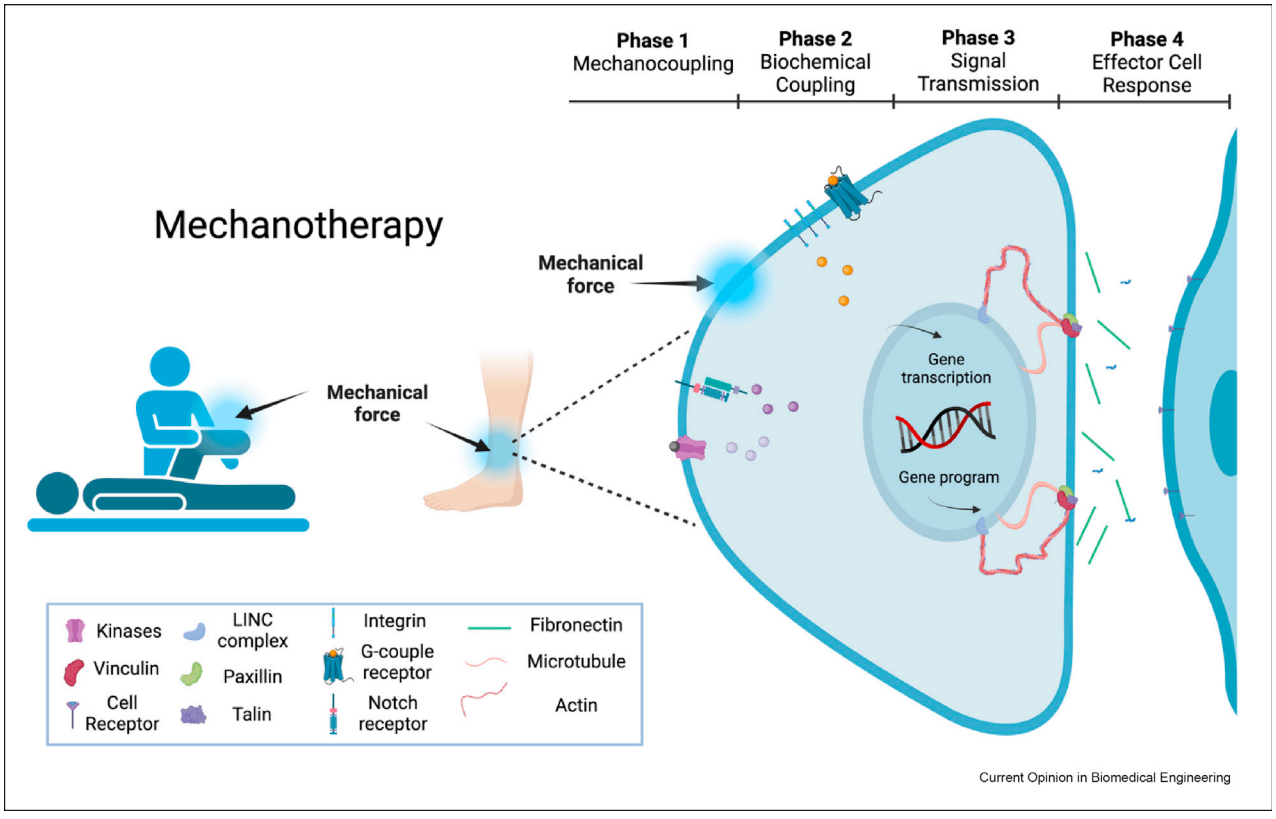
as spinal cord injuries and stroke), and degenerative diseases (such as osteoarthritis) [4]. By now, it is well established that mechanical loading and unloading translate into *cellular and molecular level* responses, subsequently affecting the tissue responses. For instance, low-magnitude, high-frequency mechanical stimulation enhances bone mass and muscle regeneration in young individuals [3,6,9] while deconditioning (unloading) of bone or spine due to prolonged bed rest and microgravity exposure initiates muscle atrophy and disc degeneration [10,11]. Yet, it is still unclear how cellular responses can be modulated using well-tailored regenerative rehabilitation strategies toward tissue regeneration and recovery. Toward this end, first, it is important to understand the phases in translating mechanical forces into biochemical responses at the cellular level to improve the field of regenerative rehabilitation.

Four distinct phases convert external mechanical stimuli into a biochemical signal, leading to tissue repair and regeneration as depicted in Figure 1: Mechanocoupling, Biochemical coupling, Signal Transmission, and Effector Cell Response [12].

During the mechanocoupling phase, the cell senses the mechanical cues from the external environment within milliseconds [13] and initiates the biochemical coupling phase. In biochemical coupling, the cells generate biochemical signals using various signaling pathways to originate changes in gene transcription.

In the mechanocoupling and biochemical coupling phases, the receptors on the cell membranes work as mechanosensors to detect the mechanical forces and activate the intercellular signaling pathways [14]. The key mechanosensors are integrins, mechanosensitive ion channels, primary cilia, and cadherins. The primary cilia microtubule-based structure extends from the surface to detect fluid flow and shear forces [15]. Once extracellular mechanical forces activate the cilia, they can influence the Signal Transducer and Activator of the Transcription (STAT) pathway through various mechanisms, including Hedgehog Signaling. The cadherin can modulate intracellular signaling pathways in response to mechanical forces by activating the Wnt signaling pathway [6]. It is well-established that these orchestrated events guide the MSK tissue repair upon mechanotherapy and regenerative rehabilitation exercises. Yet, the knowledge gap still exists in how cell-type specificity and timeliness of mechanical loading play a role in mechanotherapy and regenerative rehabilitation effectiveness. It is important to note that the timing of mechanotherapy is crucial. Different mechanotherapies may be most beneficial at specific stages of recovery. For

Figure 1



Mechanotransduction phases are initiated upon mechanical loading in mechanotherapy. Created with BioRender.com.

example, if a particular mechanotherapy has been demonstrated to promote macrophage recruitment, it may be most effective in the early stages of recovery when inflammation and immune responses are critical. In contrast, using a pro-inflammatory therapeutic might disrupt the healing process during the restorative processes in the latter stages of recovery [2].

Furthermore, cells can sense various mechanical forces, including but not limited to shear force, compression, and tension [16]. These forces play a significant role in shaping the mechanotransduction process and guiding cellular responses. For example, shear forces can affect the mechanosensitive ion channels, leading to changes in intracellular calcium levels and subsequent downstream signaling pathways [17,18]. Understanding the specific mechanical forces involved in mechanotransduction is essential for developing precise and effective regenerative rehabilitation strategies that align with the needs of the injured tissue. The orchestrated events in mechanotransduction guide musculoskeletal tissue repair upon mechanotherapy and regenerative rehabilitation exercises. Yet, a knowledge gap still exists in how cell-type specificity, timing, and the nature of mechanical loading play a role in mechanotherapy and regenerative rehabilitation effectiveness. Addressing these aspects is fundamental to advancing our understanding of this field.

Importance of cells mechanoresponsiveness for enhanced regenerative rehabilitation outcome

The application of targeted mechanical loading during mechanotherapy exercises in regenerative rehabilitation is rooted in the principle of cell-type specificity. This fundamental concept underscores the importance of targeting treatment options to the specific types of cells involved. Upon injury, the body initiates a well-orchestrated healing process involving four consecutive phases: hemostasis/coagulation, inflammation, proliferation, and remodeling/maturation [19]. Various cell types predominate during these phases, each displaying unique mechanosensitivity or mechanoresponsiveness. Moreover, it's worth noting that cells respond to mechanical loading dimensionality-dependently. Recent research, such as the study by Man, K [20], has shed light on how the dimensionality of mechanical cues can significantly influence cellular responses. The dimensionality effect is an important consideration, as it can impact how different cell types respond to mechanical loading based on factors like the direction and magnitude of the force and the dimension of the cellular microenvironment [20].

Due to the dominance of different cell types in distinct stages of healing and the dimensionality effect, it's important to recognize that applying the same mechanical loading amplitude can yield varying outcomes depending on the specific stage of the healing process [21]. In tissue repair, the cellular milieu is vast and diverse, involving well-discussed cell types and lesser-known contributors. For example, resident stromal cells, including fibroblasts, endothelial cells, and various immune cells, play crucial roles [22–24]. Endothelial cells are the initial responders that secrete molecules into circulation, initiating immune cell invasion and tissue repair processes. Furthermore, immune cells such as T cells also communicate with macrophages, orchestrating the termination of the immune response and transitioning towards the restorative phase [24]. This intricate interplay among various cell types highlights the complexity of the healing process and the importance of understanding their mechanoresponsiveness. In addition to the traditionally discussed macrophages, fibroblasts, and mesenchymal stem cells, a comprehensive understanding of the roles of resident stromal cells, endothelial cells, and the immune cell populations, including T cells and mononuclear cells, is essential for appreciating the scale of different cell types involved in tissue repair.

The uniqueness of cell mechanical responsiveness in each healing stage can significantly influence the response to regenerative rehabilitation and, consequently, the results achieved. Considering their importance in tissue regeneration, the responses of macrophages, fibroblasts, and mesenchymal stem cells to mechanical loading are discussed below, and representative studies are tabulated in Table 1.

Mechanosensitivity of macrophages

A convincing body of clinical evidence states that innate immune cells are critical regulators in musculoskeletal (MSK) tissue regeneration during rehabilitation [35]. Among the innate immune cells, macrophages are recognized as key elements for the inflammatory response and tissue healing [36]. The macrophage-depleted animal studies demonstrated that bone [37], muscle [36,38], and tendon [39] tissues do not heal following an injury without the direct involvement of macrophages. Upon injury, the circulating blood monocytes extravasate into the tissue and differentiate into naïve macrophages (M0), which concomitantly differentiate into pro-inflammatory macrophages (M1) to stimulate the precursor cell proliferation through secretion of pro-inflammatory molecules, including TNF-α, IL6, IL1β and phagocytize the tissue debris. Following the initial inflammatory phase, macrophages can alter their metabolic functions and polarize from a pro-inflammatory phenotype to a healing/growth-promoting phenotype or anti-inflammatory macrophages (M2) [40]. These sequential and transient phenotypic changes in macrophages either contribute to or hinder MSK tissue regeneration, depending on the microenvironment circulating the macrophages. Developing

Table 1

Summarized studies investigating the effect of mechanical loading as a treatment for regenerative rehabilitation in musculoskeletal tissues.

	Mechanical Loading parameters	Species and Dimensionality	Targeted Tissue	Role in Regenerative Rehabilitation	Ref.
Fibroblasts	10%–150 % strain 36min for 3 days	Mouse (3D)	Musculoskeletal tissues (soft, hard tissues)	Stretch and ECM stiffness positively affect proliferation, polarization, and differentiation of cell types towards regeneration	[25]
	4 %, 8 %, 12 % strain with 0.1 Hz, 2 h/day for 7 days	Human (3D)	Musculoskeletal tissues	Mechanical strain exerted on fibroblasts can initiate autocrine and paracrine tissue healing in a strain amplitude dependent manner.	[26]
	3 %, 6 %, and 18 % with 1Hz, 0.5Hz or 0.1 Hz for 4–24h.	Rabbits (3D)	Intervertebral discs	Moderate tensile strain at low frequencies benefits an anti-catabolic effects of the annulus fibrosus tissue	[27]
	2 % and 5 % strain with 1 Hz for 1 h/day for 15 days	Human (3D)	Ligament Tissue	Increased ligament matrix in ACL-fibroblast positively influences by the magnitude of stretching.	[28]
Stem cells	5 % strain, 6 h/day, 10times/min	Rat-marrow MSC (2D)	Bone and adipose tissues	Appropriate mechanical loading can enhance osteogenic differentiation of MSc, exercise can promote bone growth and impede maturation of adipocytes.	[29]
	2 % and 5 % strain with 1 Hz for 1 h/day for 15 days	Human bone-marrow MSC (3D)	Ligament Tissue	Magnitude of stretching (amplitude) determines the positively effect towards ligament matrix secretion and ACL regeneration	[28]
	3 %, 6 %, 12 % strain at 0.1 Hz or 1Hz for 2 h/day for 7 days	Human Adipose (3D)	Intervertebral discs	Optimized mechanical loading induce Annulus fibrosus-like cells toward IVD repair and regeneration	[30]
Macrophages	3 %, 6 %, 12 % strain with 0.1Hz for 2 h	Human pro-monocytic cell line (3D)	Blood-derived	Response of macrophages to mechanical loading is not only contingent on their sub-phenotype but varies with the amplitude of strain applied.	[31]
	0–10 % strain for up to 6h	Mouse-derived naïve macrophages (3D)	Musculoskeletal tissue	Dynamic strain mechanism has an effect of intercellular fibroblast-macrophage communication through ECM.	[32]
	1Pa at 0.5Hz for 8 days	Human (3D)	Musculo-vascular tissues	Mechanical cues and cell–cell interplay affects the inflammatory environment during early stages to tissue regeneration	[33]
	20 % strain for 16h	Human (3D)	Bone	Mechanical strain has an osteolytic potential for macrophages	[34]

effective regenerative rehabilitation therapies for MSK tissue regeneration depends on elucidating the mechanosensitivity of macrophages and understanding how mechanical loading modulates the phenotypic switch towards tissue healing (anti-inflammatory macrophages) phenotype [41] upon mechanical loading.

It's worth noting that various signaling molecules and the local microenvironment influence macrophage polarization. These factors, along with mechanical loading, collectively impact the therapeutic outcomes. Recent findings challenge the conventional belief that mechanical loading primarily impacts the formation and remodeling of the extracellular matrix [42]. For instance, after just five days of mechanotherapy exercises lasting as short as 30 min per day, a significant downregulation of pro-inflammatory gene expressions (such as IL-1β, TNF-α, and IFN-γ) was noted in the mechanically loaded tendons, unlike immobilized counterparts, where botulinum toxin A (Botox) injection was employed [43,44].

With the current clinical mechanotherapy exercises, while becoming more effective, the mechanistic understanding of how mechanical loadings exerted on MSK tissue modulate macrophage differentiation can further enhance the positive clinical outcomes of therapy [31]. Considering the frequency of MSK tissue injuries and their social and economic consequences, it becomes important to develop informed and effective clinical mechanotherapy modalities for MSK tissue healing For designing such modalities, one needs to know how mechanical loading with various amplitudes and frequencies and the influence of signaling molecules and the local microenvironment affect macrophage polarization and, consequently, MSK tissue healing [16]. Several prominent studies have been conducted in this direction. For instance, a cyclic stretch of 4 % strain at 1Hz for 24 h promotes the secretion of inflammatory genes such as IL-6, IL-8, and TNF-α in naïve macrophages. This mechanical loading rapidly induced the immediate early response of c-fos, c-jun, and MMPs genes, demonstrating that human monocytes/macrophages respond to mechanical loading with selective augmentation of MMPs and enhancing the proteolytic activity of macrophages within repairing tissues. It is important to understand how mechanical loading, as a component of mechanotherapy exercises, influences the macrophage phenotype, particularly its orientation toward pro-inflammatory lineages. This understanding represents a crucial step in advancing our knowledge of regenerative rehabilitation.

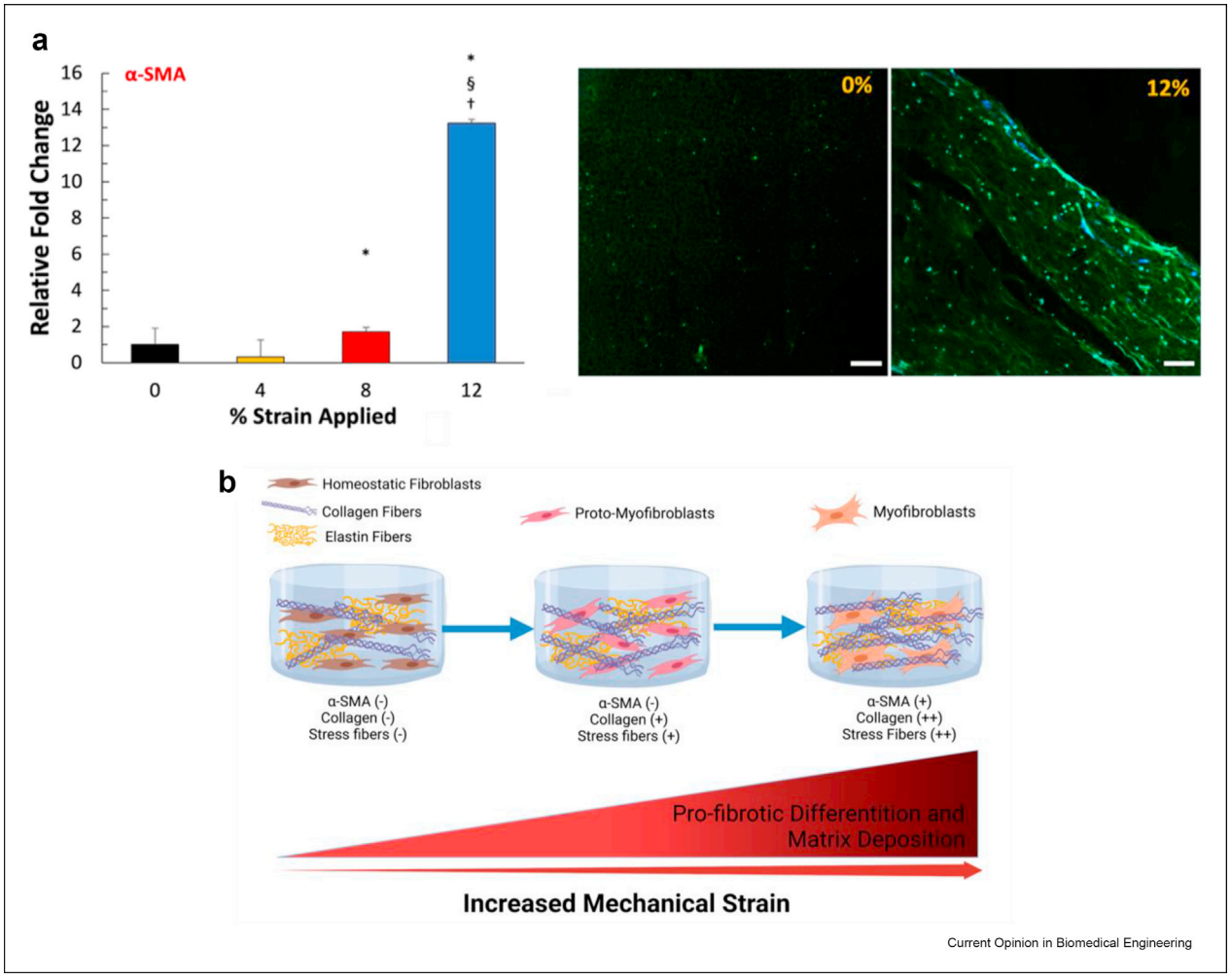
Mechanosensitivity of fibroblasts

Fibroblasts participate in the intricate interplay between mechanical forces and regenerative tissue repair [45]. In response to mechanical stimulation, fibroblasts show a varied response involving upregulated proinflammatory and profibrotic genes [26]. Similarly, these cells undergo molecular changes, including proliferation, migration, and differentiation into contractile myofibroblasts. The transition of fibroblasts to myofibroblasts is crucial in fibrotic tissue formation during the healing process. Efforts have been made to understand the loading amplitude influencing this transition, as fibroblasts are commonly used in musculoskeletal tissue regeneration [46–48]. While the 3D collagen lattice models are widely used to study fibroblast-ECM interactions and myofibroblast differentiation, a very few studies consider the mechanical loading exerted on the ECM and cells, which is significant for positive clinical outcomes [48,49]. Figure 2 demonstrates data from a representative study investigated the role of mechanical forces acting on the fibroblast-laden tissue on onset and progression of fibroblast-to-myofibroblast transition (FMT) [26].

Understanding how different amplitudes of mechanical loading applied to a physiologically relevant in vitro environment affects the transition from normal tissue repair to fibroblast-to-myofibroblast is crucial for developing effective therapies for musculoskeletal tissues subject to constant mechanical loading [26]. There are still questions about how the degree of mechanical loading and changes in matrix properties impact this transition. This orchestrated response to mechanical loading underscores the complexity of molecular pathways that initiate fibroblast mechanotransduction. While certain pathways remain examined, recent studies [32,45] have witnessed substantial progress in understanding the integral cellular structure, genes, and signaling cascades that facilitate fibroblast response to mechanical stimuli. For instance, Baum and Duffy explained the mechanosensitive phenomenon characterized by cell traction forces (CTFs) generated through intricate coordination of the cellular cytoskeleton. This phenomenon is crucial for wound contraction during the fibroblast to myofibroblast transition. Myofibroblasts organize granulation tissue in its late stage, exerting contractile forces that facilitate wound closure [26,50]. This mechanical coordination originates from the sliding interactions of ATP-powered actin-myosin filaments, transmitting tension via focal adhesions that anchor to the ECM [26]. Notably, actin polymerization at the leading edge of migrating cells contributes to CTF generation.

As mentioned, focal adhesion kinase (FAK) is a central kinase receptor and conductor of mechanical input and cellular responses (Figure 1). Mechanical loading, such as tension, stretching, or compression, can activate FAK during mechanotherapy. This integrin-dependent autophosphorylation of FAK activates kinases within the Src family, initiating downstream signaling cascades. FAK's pivotal role is underscored by studies demonstrating its influence on cell migration, mechanical responses, and scar formation on fibroblast and myofibroblast transition

Figure 2



(a) Excessive mechanical strain amplitude induces fibrosis **(b)** Relationship between the amplitude of mechanical strain applied on the tissue and fibroblast-to-myofibroblast (FMT) transition. Increased mechanical strain leads to proto-myofibroblasts forming and subsequent differentiation to myofibroblasts. The data and images are from *"Mechanoresponsive regulation of fibroblast-to-myofibroblast transition in three-dimensional tissue analogues: mechanical strain amplitude dependency of fibrosis*" [26].

[22]. For example, FAK-knockout mice exhibit reduced inflammation and fibrosis in a murine hypertrophic scar model [51], highlighting FAK's involvement in pathologic scarring. Therefore, it is particularly important to investigate how mechanical loading, as a viable option for mechanotherapy, affects the fibroblast—myofibroblast transition toward tissue regeneration.

Mechanosensitivity of mesenchymal stem cells (MSCs)

The intricate interplay between cellular mechanics and biological processes has also gained prominence in stem cell biology and regeneration, particularly in mesenchymal stem cells (MSCs). MSCs, often called the architects of tissue repair and regeneration, exhibit an extraordinary ability to differentiate into various cell lineages [1,52], contributing to maintaining tissue homeostasis and facilitating wound healing. A significant breakthrough in understanding MSC behavior has been the recognition of their ability to be mechanosensitive — the responsiveness to physical forces and mechanical cues from their environment. This mechanosensitive is pivotal in dictating MSC fate determination and differentiation, offering profound implications for regenerative and rehabilitation [1,53].

As in the case of macrophages and fibroblasts, the ECM orchestrates MSC behavior, intricately regulating self-renewal, pluripotency, and lineage specification. The mutual communication between MSCs and their ECM is a two-way path. MSCs secrete bioactive molecules that influence the environment and exert mechanical forces through their cytoskeletal components, thereby modulating the environment in which they reside [54]. For instance, the plasticity exhibited by cancer stem cells in reorganizing their microenvironment underscores the malleable nature of the ECM. Furthermore, studies illuminating the maintenance of pluripotency in naïve stem

cells emphasize the impact of mechanotransducers [55]. Their transducers communicate signals that regulate vital pathways like WNT/β-catenin and control the expression of key markers such as E-cadherin, steering the fate of MSCs towards self-renewal and multipotency [55].

The pivotal role of mechanical cues in lineage specification emerges as a central question in MSCs mechanobiology. Many prominent studies have already proved that human MSCs are mechanoresponsive. The mechanical loading amplitude and frequency dictate the lineage commitment of hMSCs towards tenogenic, myogenic, chondrogenic, and osteogenic differentiation [30,56]. One study by Azizi, P. et al. [57] utilized a fluid–structure interaction (FSI) model to simulate mechanical stimulation on 3D hydrogel scaffolds seeded with hMSCs. It was discovered that cell fate was strongly impacted by the dynamic compressive loading's magnitude. While the number of cells differentiating into bone tissue decreased as the compression amplitude increased, within a certain range of compression, the differentiation of cartilage cells increased and then declined. Another study highlighted the multidirectional differentiation capacity of bone marrow MSCs [58] by examining how they responded to mechanical loading and motility. The effects of locomotion-induced mechanical stimulation on BMSC migration, proliferation, and differentiation provide insight into the potential benefits of proper exercise regimes for maintaining bone health.

To explore the effects of mechanical stimuli on stem cells, particularly mesenchymal stem cells (MSCs), specialized devices such as stretch stimulation devices have become instrumental in replicating the physical changes these cells experience in their natural environment. Understanding how mechanical stress influences MSC behavior and differentiation is crucial for advancing regenerative rehabilitation strategies. In addition, a study by Uzieliene, I. et al. [59] looked at how chondrocytes and hMSCs responded to mechanical stress in 3D hydrogels based on chondroitin sulfate. Even while chondrocytes expressed more genes specific to cartilage, they were more vulnerable to mechanical stress. hMSCs, on the other hand, showed more consistent regulation of intracellular calcium levels, indicating their benefit for cartilage regeneration. Together, these findings highlight the complex relationship between mechanical loading and hMSC differentiation. As we delve deeper into the intricate world of mechanotransduction, these innovative devices continue to shed light on how mechanical stimuli can enhance tissue repair and rehabilitation, opening new therapeutic applications.

Extracellular vesicles as mechano-therapeutic effectors

As our understanding of regenerative rehabilitation grows, the interaction between mechanical forces and biological responses is crucial in maximizing tissue repair and regeneration. This investigation emphasized the potential significance of extracellular vesicles (EVs) and how mechanical loading might affect the formation and composition of EVs, thus affecting the regenerative process. Examining these dynamics may lead to the creation of focused treatments that improve tissue healing results by boosting regeneration signals mediated by EVs.

Moreover, in addition to the sheer number of EVs, it is critical to investigate how mechanical loading affects the makeup of EV cargo. The EVs extracted from the mechanically stimulated cells are packed with bioactive chemicals to further support tissue regeneration and repair. For instance, as shown by Wang. et al. [60], EVs released by mechanically strained fibroblasts may contain components that promote collagen synthesis and tissue remodeling. This study sheds light on the molecular pathways behind regeneration rehabilitation by examining EV cargo under various mechanical environments. With the increasing depth of our knowledge regarding the effects of mechanical loading on EV secretion and function, the possibility of creating customized EV-based treatments for regeneration rehabilitation is becoming more viable. According to the study by Guo S. et al. [61], these therapies might entail separating and engineering EVs from mechanically stimulated cells to increase their capacity for regenerative medicine. Furthermore, the stage of tissue repair and the current mechanical loading circumstances may influence the timing and dosage of EV-based therapies. Although, these studies reveal the potential of EVs in regenerative rehabilitation, it is important to note that EV-based therapies are still emerging techniques that require further study.

Conclusion

This review has underscored the pivotal role of mechanome-guided strategies in shaping the future of regenerative rehabilitation. The mechanosensitivity of cells to mechanical loading during the regenerative rehabilitation process is a central theme of this review. From macrophages orchestrating inflammation and healing to fibroblasts bridging the gap between injury and tissue repair and mesenchymal stem cells offering plasticity for regeneration, cells exhibit distinct mechanoresponsiveness during different phases of tissue healing. By exploring the mechanosensitivity of various cell types and their responses to mechanical loading, this field offers a pathway for designing more effective regenerative rehabilitation strategies. While the future of regenerative rehabilitation is filled with boundless possibilities, mechanome-guided regenerative rehabilitation holds immense promise for accelerating tissue healing and improving the quality of life for individuals with musculoskeletal injuries and degenerative diseases.

Author's contribution

E.Y.A. and D.J. conceived the main idea. E.Y.A. and D.J. wrote the main manuscript text. All authors reviewed the manuscript.

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In this study using a 3D-engineered muscle model, the authors showed that mechanical unloading led to significant muscle atrophy, with muscle weight, length, twitch contractile force, and myosin heavy chain expression in the "stretched-off" group (OFF) decreasing by approximately 38.1% to 75.0% on days 2 and 7 compared to the "stretched-on" group (ON). The primary mechanism of atrophy was found to be the suppression of muscle protein synthesis (MPS), with a reduction ranging from approximately 38.5% to 51.1%, while muscle protein breakdown (MPB), particularly through the ubiquitin-proteasome pathway, was not significantly affected.

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The authors discuss the role of mechanosensitive proteins YAP and TAZ (YAP/TAZ) in regulating inflammation and immunity in innate immune cells. It discusses how YAP/TAZ plays a role in various aspects of inflammatory diseases, wound healing, and tissue regeneration, emphasizing their potential as therapeutic targets for managing inflammatory conditions.

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The article discusses the significance of mechanical stress in wound healing and scar formation, highlighting the cellular mechanisms involved in this process. It reviews proteins and pathways, such as focal adhesion kinase, RhoA/ROCK, the Hippo pathway, YAP/TAZ, and Piezo1, and how their modulation can reduce scar formation and improve wound healing.

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