Research Article

Convergent Regenerative Strategies in PM&R for Musculoskeletal and Hair Restoration: Integration of PRP, Exosomes, and Physical Modalities

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Abstract

Regenerative medicine has emerged as a transformative approach for both musculoskeletal disorders and hair follicle dysfunction by targeting shared biological mechanisms underlying tissue repair and renewal. Conditions such as tendinopathies, osteoarthritis, and alopecia contribute substantially to physical morbidity and psychosocial burden, while conventional therapies often provide limited or symptomatic relief. This Physical Medicine and Rehabilitation-centered review synthesized evidence on convergent regenerative pathways involved in musculoskeletal healing and hair follicle restoration, with a focused analysis of platelet-rich plasma, exosomes and cell-free biologics, and physical modalities, including low-level laser therapy and mechanotransduction. Across both tissue systems, these modalities modulate stem cell activity, angiogenesis, inflammatory signaling, and extracellular matrix remodeling through shared molecular pathways, including Wnt/β-catenin, TGF-β, IGF-1, PDGF, and VEGF signaling. Despite tissue-specific differences in cellular architecture and repair demands, overlapping regenerative mechanisms enable translational application of biologic, photo-biomodulatory, and mechanical therapies across orthopedic and dermatologic contexts. This review highlights clinical evidence, practical considerations, and regulatory challenges, while identifying gaps in standardization, dosing, and outcome measures. By framing hair follicle restoration and musculoskeletal healing within a unified regenerative paradigm, physical medicine and rehabilitation is positioned to bridge these traditionally distinct domains and advance biologically driven, minimally invasive therapies aimed at true tissue regeneration rather than symptom modulation alone.

Keywords: Exosomes; Hair follicle regeneration; Low-level laser therapy (LLLT, photobiomodulation); Mechanotransduction, Musculoskeletal healing; Physical modalities; Platelet-rich plasma (PRP); Regenerative medicine

Introduction

Regenerative medicine represents a paradigm shift in treating musculoskeletal disorders and hair follicle dysfunction by addressing the fundamental limitations of conventional therapies through biologically driven tissue repair mechanisms. Musculoskeletal conditions such as tendinopathies and osteoarthritis contribute to substantial morbidity through chronic pain and functional impairment, while hair loss disorders including androgenetic alopecia and alopecia areata impose significant psychosocial burdens [1-2]. Conventional treatments for both categories often demonstrate limited efficacy, undesirable side effects, or require invasive interventions, necessitating the development of novel therapeutic strategies [3].

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This review synthesizes evidence on regenerative pathways common to musculoskeletal and hair follicle healing, focusing on modalities applicable to physical medicine and rehabilitation practice. The objective is to identify shared molecular mechanisms, examine clinical applications across both domains, and propose opportunities for translational innovation.

Four primary regenerative modalities form the framework of this analysis. Platelet-rich plasma (PRP), an autologous blood concentrate enriched with growth factors and cytokines, has demonstrated regenerative capacity in tendon, cartilage, bone, and hair follicle tissues [4-8]. Exosomes function as intercellular messengers that facilitate tissue regeneration across multiple systems including musculoskeletal and dermatologic structures [9-11]. Low-level laser therapy (LLLT) enhances cellular metabolism and tissue repair in both orthopedic rehabilitation and hair restoration contexts [1]. Mechanotransduction, which is the conversion of mechanical forces into biochemical signals, drives tissue adaptation and represents an increasingly recognized therapeutic mechanism in both musculoskeletal and follicular biology (Figure 1).
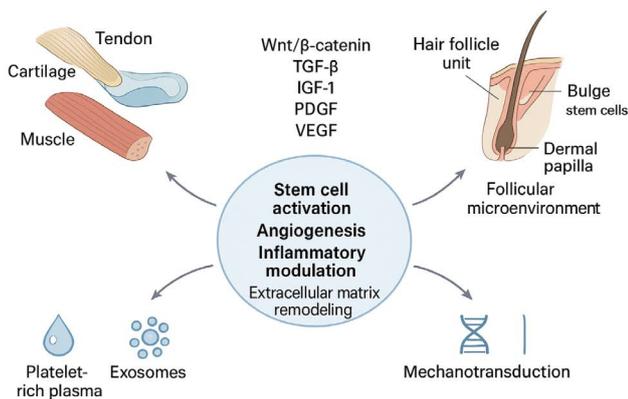
Figure 1: Shared regenerative modalities including platelet-rich plasma, exosomes, low-level laser therapy, and mechanotransduction converge on common molecular pathways that regulate stem cell activity, angiogenesis, inflammation, and extracellular matrix remodeling in both musculoskeletal tissues and hair follicles.

Through integrated analysis of these modalities, this review elucidates the convergent regenerative pathways and evidence-based clinical strategies that bridge musculoskeletal healing and hair follicle restoration within the scope of physical medicine and rehabilitation (PM&R).

II. Shared Biological Foundations of Regeneration

Regenerative medicine in musculoskeletal and hair follicle systems operates through convergent biological principles: cellular proliferation and differentiation, extracellular matrix remodeling, angiogenesis, and inflammatory modulation. These processes are coordinated by growth factors, cytokines, and stem cell populations that respond to therapeutic interventions including platelet-rich plasma, exosomes, low-level laser therapy, and mechanotransduction.

Mesenchymal stem cells (MSCs) constitute the primary cellular mediators in both tissue systems, responding to biochemical and mechanical cues within specialized niches. PRP provides a concentrated growth factor milieu, including platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), and insulin like growth factor 1 (IGF-1), that activates stem cell proliferation, guides differentiation, and promotes vascularization [6-8], [12-13]. Exosomes complement these effects through paracrine signaling, delivering microRNAs and proteins that regulate regenerative cascades [14].

Stem cell niches exhibit both commonalities and specialization. Musculoskeletal MSC populations reside in mechanically responsive environments that mediate injury repair and tissue homeostasis [8], [12]. Hair follicle stem cells, concentrated in the bulge region, drive cyclical regeneration with distinct epithelial and mesenchymal components [1],[15]. Despite functional differences, continuous homeostasis versus cyclical renewal, both niches respond to analogous molecular signals and growth factor stimulation.

Several key pathways mediate regeneration across both systems. Wnt/β-catenin signaling drives stem cell activation and lineage commitment, regulating dermal papilla function and anagen initiation in hair follicles while directing osteogenesis and chondrogenesis in musculoskeletal tissues [14]. TGF-β modulates the balance between regenerative repair and fibrotic responses, controlling inflammation and cellular differentiation in both contexts [8], [12]. The growth factors IGF-1, PDGF, and VEGF promote cellular proliferation, survival, and angiogenesis essential for both follicular cycling and musculoskeletal repair [5]. Precise inflammatory regulation proves critical, with PRP and exosomes facilitating transitions toward anti-inflammatory, pro-regenerative microenvironment [7].

Physical medicine modalities further engage these pathways. LLLT activates Wnt/β-catenin signaling and enhances mitochondrial function, stimulating regeneration in both tissue types [1]. Mechanotransduction through controlled mechanical loading triggers stem cell activity and growth factor secretion, amplifying endogenous repair mechanisms across musculoskeletal and follicular systems.

III. Platelet-Rich Plasma (PRP)

Platelet rich plasma represents an autologous biological therapy employing convergent regenerative mechanisms across musculoskeletal and hair follicle systems. PRP contains concentrated platelets, growth factors (including

VEGF, PDGF, and TGF-β), cytokines, and extracellular vesicles that collectively facilitate tissue repair through angiogenesis, immunomodulation, matrix synthesis, and cellular recruitment. These mechanisms support tendon, cartilage, and bone repair in musculoskeletal applications while promoting follicular stem cell activation and dermal papilla cell proliferation in hair restoration [4], [7], [16].

In musculoskeletal medicine, PRP has been applied to tendinopathies, osteoarthritis, and muscle injuries. The American Medical Society for Sports Medicine recognizes that PRP modulates inflammation and healing through rapid growth factor release, with the strongest clinical evidence supporting its use in tendinopathy and osteoarthritis [17]. PRP accelerates the wound healing cascade, enhances cellular recruitment, and facilitates matrix remodeling in musculoskeletal tissues. Evidence supports its efficacy particularly in chronic tendon injuries and mild to moderate osteoarthritis [6].

For hair restoration, PRP has demonstrated efficacy in treating androgenetic alopecia through activation of dermal papilla cells. Multiple randomized controlled trials and systematic reviews show that PRP increases hair count and density in androgenetic alopecia, with histologic confirmation of enhanced follicular proliferation and dermal papilla cell activation [2], [5], [18], [19], [20]. The mechanism involves promoting hair follicle stem cell proliferation, extending the anagen phase, and upregulating growth factors essential for folliculogenesis [1], [21]. Sonicated PRP preparations may further amplify stem cell activation and support de novo follicle regeneration [21].

Both musculoskeletal and hair follicle applications share core regenerative pathways, including growth factor mediated angiogenesis, immunomodulation, and matrix synthesis. However, tissue specific responses distinguish the two: musculoskeletal healing relies more heavily on fibrinolytic processes and mesenchymal stem cell recruitment, whereas hair follicle restoration depends primarily on follicular stem cell activation and dermal papilla signaling [16]. Preparation heterogeneity and the absence of standardized protocols remain significant challenges across both domains, underscoring the need for further research and consensus development [6].

IV. Exosomes and Cell-Free Biologics

Exosomes and cell free biologics serve as key mediators of regenerative processes in both musculoskeletal and hair follicle systems, functioning primarily through paracrine signaling and the delivery of bioactive cargo including microRNAs, proteins, and lipids. These extracellular vesicles facilitate intercellular communication and regulate cell proliferation, migration, anti-apoptosis, angiogenesis, and immunomodulation. In musculoskeletal tissues, exosomes

derived from stem cells or mesenchymal stromal cells enhance endogenous cell functions, promote tissue repair, and regulate inflammation by transferring specific microRNAs and growth factors that activate regenerative pathways [22-27]. Within the hair follicle, exosomes influence cycling and regeneration by stimulating dermal papilla cells and hair follicle stem cells, supporting angiogenesis, and modulating the local immune environment [28-31].

Preclinical evidence for the use of exosomes in musculoskeletal healing has been substantial, with studies demonstrating accelerated bone, cartilage, and tendon repair, reduced inflammation, and improved functional outcomes. Engineering strategies that load exosomes with therapeutic microRNAs or integrate them with biomaterials for sustained release have further enhanced their efficacy and tissue specificity [24]. Clinical translation remains in progress, with ongoing challenges related to standardization, targeting, and retention time [27].

In hair follicle restoration, exosomes derived from MSCs have shown efficacy in preclinical studies and early clinical trials for conditions such as androgenetic alopecia and nonscarring alopecias. These exosomes promote hair growth by activating dermal papilla cells, supporting stem cell function, and delivering microRNAs that regulate follicle cycling and immune response [28]. Pilot clinical trials have reported encouraging safety and feasibility data, though larger studies are necessary to confirm efficacy and optimize dosing protocols [30].

MicroRNA and paracrine signaling pathways represent critical links between musculoskeletal and hair follicle regeneration. Exosomes deliver microRNAs that modulate Wnt/β-catenin, TGF-β, and other signaling cascades essential for stem cell activation, angiogenesis, and tissue remodeling in both systems [29], [31]. Paracrine effects mediated by cytokines, chemokines, and growth factors support repair and homeostasis across tissue types [31].

While musculoskeletal and hair follicle systems share fundamental regenerative pathways involving stem cell activation, angiogenesis, and immunomodulation driven by exosome cargo, they differ in the specific cell types targeted such as osteoblasts and chondrocytes versus dermal papilla cells and the microenvironmental requirements for tissue specific repair (Figure 2). Engineering exosomes for targeted delivery and controlled release offers a promising approach to address these differences and optimize therapeutic outcomes [24], [27].

V. Low-Level Laser Therapy

Low-level laser therapy also termed photobiomodulation (PBM), produces regenerative effects through the absorption of red and near-infrared light by cellular chromophores, primarily cytochrome c oxidase in mitochondria.
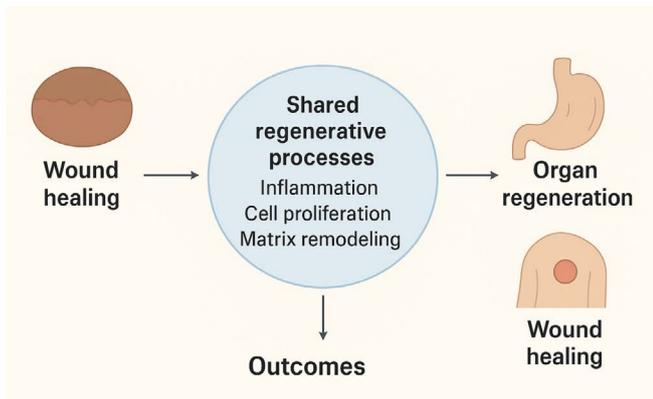
Figure 2: Conceptual diagram illustrating the shared regenerative processes linking wound healing and organ regeneration through coordinated inflammation, cellular proliferation, and extracellular matrix remodeling that drive tissue repair and functional recovery.

This interaction enhances ATP production, modulates reactive oxygen species, and activates intracellular signaling pathways, resulting in increased cell proliferation, migration, and differentiation, along with reduced inflammation and oxidative stress [32-35]. These mechanisms underpin tissue repair and regeneration across multiple organ systems.

In musculoskeletal healing, LLLT has proven effective in promoting bone and tendon repair, angiogenesis, and osteogenic differentiation of stem cells. The therapy modulates gene expression of growth factors including VEGF, FGF, and TGF-β, and influences the phases of tendon healing by promoting angiogenesis, fibroblast proliferation, and M2 macrophage activation, ultimately enhancing tissue remodeling while reducing inflammation [36-39]. Clinical evidence supports its use for pain reduction and functional improvement in conditions such as osteoarthritis, tendinopathies, and post-surgical recovery.

For hair growth, LLLT has received FDA clearance for androgenetic alopecia and demonstrated safety and efficacy in randomized controlled trials for both male and female pattern hair loss. The mechanisms involve stimulation of hair follicle stem cells, upregulation of growth factors, and modulation of the hair cycle, particularly prolonging the anagen phase [1], [40], [41]. LLLT also reduces follicular inflammation and oxidative stress, contributing to improved hair density and thickness.

Both musculoskeletal and hair follicle regeneration share therapeutic pathways involving activation of mitochondrial metabolism, upregulation of growth factors and modulation of inflammatory and paracrine signaling. Both tissues benefit from enhanced stem cell proliferation and differentiation, angiogenesis, and extracellular matrix remodeling [40]. MicroRNAs and paracrine factors are increasingly recognized as mediators of these effects, with LLLT influencing their expression to promote regenerative outcomes [38].

While musculoskeletal healing and hair follicle restoration share fundamental pathways involving mitochondrial activation, growth factor signaling, and stem cell modulation, tissue-specific differences emerge. Musculoskeletal tissues depend more heavily on collagen synthesis, matrix remodeling, and macrophage polarization, whereas hair follicle restoration centers on hair cycle regulation and follicular stem cell activation [36]. The overlap in microRNA and paracrine signaling reveals a convergent regenerative axis, yet tissue-specific responses to LLLT are determined by local cellular context and repair demands [33].

VI. Mechanotransduction and Biophysical Signaling

Mechanotransduction is the process by which cells convert mechanical stimuli into biochemical signals, influencing gene expression, cellular behavior, and tissue adaptation. This process involves the sensing of forces such as tension, compression, and shear by cellular structures (including integrins, ion channels, and the cytoskeleton), which trigger intracellular signaling cascades that regulate proliferation, differentiation, and matrix remodeling [42-43]. This fundamental principle underlies both homeostatic maintenance and regenerative responses across diverse tissues.

In musculoskeletal healing, mechanotransduction is essential to tissue repair and remodeling. Mechanical loading through exercise, physical therapy, or targeted rehabilitation activates mechanotransductive pathways that stimulate anabolic responses in bone, tendon, muscle, and cartilage. Loading induces fluid flow and strain within bone, activating osteocytes and promoting bone formation via Wnt signaling and related molecular pathways [44]. Physical therapy frameworks utilize these principles by prescribing specific movement and loading regimens to optimize tissue regeneration and functional recovery, a concept known as "mechanotherapy" [45-47]. Integrating mechanical stimuli with regenerative medicine approaches (such as stem cell therapies and biomaterial scaffolds) further enhances musculoskeletal healing by modulating the local microenvironment and cellular responses [44].

Mechanotransduction also influences hair follicle restoration. Techniques such as microneedling and negative pressure therapy induce controlled micro-injury or mechanical stress in the scalp, triggering the release of growth factors, promoting angiogenesis, and stimulating stem cell activation within the hair follicle niche.[8-9] Wound-induced hair neogenesis demonstrates how mechanical disruption of the skin can lead to de novo hair follicle formation through biophysical signaling and regenerative cascades resembling those in musculoskeletal tissues. These approaches are frequently combined with regenerative therapies (such as PRP and exosomes) to amplify follicular regeneration [5].

At the pathway level, mechanical signaling in musculoskeletal and hair follicle systems shows significant parallels. Both depend on the interplay between extracellular matrix mechanics, stem cell activation, and growth factor release to drive tissue regeneration [43]. The spatiotemporal control of mechanical cues proves critical in both contexts, influencing stem cell fate decisions and orchestrating coordinated tissue remodeling [46]. Physical medicine and rehabilitation thus serve as a bridge, applying mechanotransductive principles to optimize outcomes in both musculoskeletal and hair restoration therapies.

VII. Clinical Implications

Treatment algorithms vary considerably in their standardization and evidence base. In musculoskeletal medicine, PRP is primarily applied to tendinopathies and osteoarthritis, often as an adjunct to rehabilitation protocols, with dosing and preparation guided by consensus statements such as those from the American Medical Society for Sports Medicine [17]. In hair restoration, PRP, exosomes, and LLLT are used for androgenetic alopecia and alopecia areata, but protocols remain less standardized, showing significant variability in preparation, dosing, and frequency [20], [48], [49]. This lack of uniformity across both fields complicates direct comparison and emphasizes the need for standardized protocols and quality control measures, such as the WESS-PQR scoring system for PRP [48].

Patient response predictors include tissue type, disease chronicity, and individual biological factors. Higher initial platelet counts and proper temperature control during PRP preparation correlate with improved efficacy across tissues. In musculoskeletal applications, factors such as age, comorbidities, and injury chronicity affect outcomes [6]. For hair restoration, predictors include the type of alopecia, follicular density, and scalp vascularity [2-3]. This heterogeneity in response highlights the importance of careful patient selection and individualized treatment planning.

Safety, regulatory, and ethical considerations are particularly relevant in California. PRP and related biologics are generally safe, with minimal adverse effects reported, but preparation heterogeneity and lack of standardization introduce potential risks [48]. Regulatory oversight in California requires compliance with state and federal guidelines for biologic therapies, including documentation of preparation methods and informed consent. Ethical considerations encompass transparency in advertising, avoidance of unproven claims, and equitable access to care. Robust regulatory frameworks and standardized reporting are necessary to ensure patient safety and treatment efficacy [48].

VIII. Gaps in Knowledge and Future Directions

Despite promising results, significant gaps in knowledge remain. There is a pressing need for standardized biologic preparation and dosing. PRP and exosome therapies suffer from heterogeneity in composition and lack consensus on optimal protocols, which impedes reproducibility and comparability across studies.[20], [50] Comparative trials directly evaluating these modalities in both musculoskeletal and hair applications are scarce, limiting the ability to generalize findings and optimize treatment selection [3]. Additionally, most studies focus on symptom modification rather than true tissue regeneration, and sentinel markers of biologic potency remain poorly defined [51].

Future research should prioritize the development of standardized protocols for biologic therapies, robust comparative effectiveness trials, and the integration of emerging technologies such as gene therapy and advanced cell-based treatments. Research opportunities include elucidating the specific contributions of extracellular vesicles, optimizing mechanotransduction based interventions, and leveraging precision medicine approaches to match biologic treatments to individual patient needs [10]. Addressing these gaps will be essential for advancing regenerative medicine in both physical medicine and rehabilitation and dermatology.

IX. Conclusion

Regenerative medicine offers a unifying framework for treating both musculoskeletal disorders and hair follicle dysfunction by leveraging shared biological mechanisms that drive tissue repair. Across PRP, exosomes, low level laser therapy, and mechanotransduction, a consistent theme emerges: these modalities stimulate stem cell activity, enhance angiogenesis, modulate inflammation, and promote extracellular matrix remodeling. Despite the distinct structural and functional demands of musculoskeletal and follicular tissues, both systems rely on overlapping molecular pathways including Wnt/β catenin, TGF β, IGF 1, and PDGF to orchestrate regeneration. This convergence underscores the unique position of physical medicine and rehabilitation to integrate regenerative strategies that span orthopedic and dermatologic applications.

At the same time, meaningful challenges persist. Preparation variability in PRP and exosomes, inconsistent dosing protocols, and limited comparative clinical trials hinder widespread standardization and the ability to generalize outcomes across patient populations. Mechanical and photobiomodulatory therapies show robust promise, yet their optimal parameters remain incompletely defined. Regulatory considerations, particularly in California, further highlight the need for transparent reporting, ethical application, and rigorous quality control.

Future progress will depend on harmonizing biologic preparation methods, advancing precision-based treatment algorithms, and developing biomarkers that accurately reflect

regenerative potency. Integrating mechanotransductive insights, engineered extracellular vesicles, and emerging gene-based therapies holds potential to elevate both musculoskeletal rehabilitation and hair restoration from symptom focused care to true tissue regeneration. By bridging these traditionally separate domains, regenerative medicine positions itself to transform clinical practice through biologically informed, minimally invasive, and patient centered therapeutic innovation.

Key points

- Musculoskeletal tissues and hair follicles share core regenerative pathways involving stem cell activation, angiogenesis, inflammatory modulation, and extracellular matrix remodeling.

- Platelet-rich plasma promotes repair in both systems through growth factor–mediated effects on mesenchymal stem cells and follicular stem cells.

- Exosomes function as critical paracrine mediators, delivering microRNAs and proteins that regulate Wnt/β-catenin, TGF-β, and angiogenic signaling across tissues.

- Low-level laser therapy enhances mitochondrial metabolism, growth factor expression, and stem cell proliferation in both orthopedic rehabilitation and hair restoration.

- Mechanotransduction links physical therapy, exercise, microneedling, and mechanical loading to biologically driven regeneration through biophysical signaling.

- Despite shared pathways, tissue-specific differences exist, with musculoskeletal repair emphasizing matrix remodeling and follicular restoration emphasizing hair cycle regulation.

- Clinical protocols for PRP, exosomes, and LLLT remain heterogeneous, limiting reproducibility and comparative effectiveness across studies.

- Physical medicine and rehabilitation provide a unique framework to integrate biologics, photobiomodulation, and mechanotherapy into coordinated regenerative strategies.

- Future progress depends on standardized biologic preparation, precision-based patient selection, and biomarkers that reflect true regenerative potency.

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