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REVIEW

Biological Mechanisms and Clinical Challenges of Platelet-Rich Plasma in Chronic Musculoskeletal Pain: From Standardized Preparation to Multi-Omics-Guided Precision Therapy

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Background: Chronic musculoskeletal pain (CMP) affects over 1 billion people globally. Platelet-rich plasma (PRP) therapy has emerged as a promising regenerative approach.

Methods: This review synthesizes current literature on PRP's biological mechanisms, preparation techniques, clinical efficacy, and ethical challenges, with a focus on multi-omics integration for personalized therapy.

Results: PRP promotes tissue repair through growth factor release and immunomodulation, but clinical translation is hampered by preparation variability, lack of predictive biomarkers, and ethical concerns. Multi-omics approaches (genomics, proteomics, metabolomics) offer potential for efficacy prediction and treatment personalization.

Conclusion: Standardization of PRP preparation and rigorous long-term trials are urgently needed. Multi-omics-guided strategies may enhance precision in PRP therapy for CMP.

Keywords: platelet-rich plasma, chronic musculoskeletal pain, tissue regeneration, immunomodulation, multi-omics, precision medicine

Introduction

Chronic musculoskeletal pain (CMP), as a global public health challenge, has a prevalence rate of 20%-33%, affecting more than 1 billion people worldwide.[1] In the past two decades, CMP has become the leading cause of disability worldwide and the incidence rate may continue to rise.[2] Epidemiological data shows that women, the elderly, and socioeconomically vulnerable groups are at significantly higher risk.[3,4] Low back pain and knee pain are the most common types, often accompanied by functional decline, depression, and a decrease in quality of life.[5,6]

The clinical treatment of such patients currently faces an undeniable dilemma - the limitations of existing treatment methods are gradually becoming apparent in practice.[7] Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for analgesia, but long-term use increases the risk of gastrointestinal ulcers, renal injury, and cardiovascular events.[8] Opioids, although effective in the short term, are highly controversial due to their high addiction potential and risks of overdose and death.[9,10] Neither class of drugs can reverse tissue degeneration, only providing temporary symptom relief, which highlights the necessity of collaborative therapy combining tissue repair and pain regulation.[11]

Platelet-rich plasma (PRP) therapy emerged in the 1990s, initially applied in sports medicine for treating acute injuries such as tendinitis and ligament injuries.[12] Its core mechanism involves concentrating autologous platelets through centrifugation to release growth factors, promoting tissue repair and anti-inflammation. With deepening research, PRP application has gradually expanded to chronic musculoskeletal pain management, including osteoarthritis,

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discogenic pain, etc.[13] Its bioactive regulatory mechanisms involve two aspects: first, growth factors activate mesenchymal stem cell differentiation to promote cell proliferation and matrix synthesis; second, inhibiting the Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway reduces the expression of pro-inflammatory factors like Interleukin-1 beta (IL-1β) and Tumor Necrosis Factor alpha (TNF-α), alleviating chronic inflammation.[14–16]

Despite these advancements, PRP therapy faces significant challenges in standardization and clinical translation.[17] This review aims to systematically summarize the biological mechanisms and clinical challenges of PRP in the treatment of chronic musculoskeletal pain, with a focused exploration of future directions, from standardized preparation protocols to multi-omics-guided efficacy prediction. The goal is to provide a comprehensive yet targeted analysis that bridges current scientific understanding with clinical applications, ultimately offering insights for more effective and personalized PRP therapies.

Biological Characteristics and Preparation Technology Status of PRP

PRP is a plasma product obtained by separating autologous whole blood through centrifugation and other methods, with a platelet concentration typically 2–6 times higher than that of whole blood. This special component composition endows PRP with unique biological properties, making it show important value in the field of tissue repair. PRP contains abundant bioactive substances, and the core components include various growth factors, such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), vascular endothelial growth factor (VEGF), insulin-like growth factor (IGF), etc.[18,19] These growth factors are released after platelet activation, and can drive the tissue repair process by regulating cell proliferation, differentiation, migration, and extracellular matrix synthesis.[20] In addition, PRP also contains white blood cells, cytokines (such as interleukin, tumor necrosis factor, etc)., fibrinogen, and various active enzymes, which together form a complex network of bioactive substances and play a synergistic role in inflammation regulation, immune regulation, and coagulation mechanisms.[21] Recent studies have also found that emerging components in PRP, such as platelet-derived exosomes and microRNAs (miRNAs), can participate in intercellular communication by transmitting information molecules such as nucleic acids and proteins, further expanding the biological functions of PRP.[22,23]

In terms of preparation technology, the acquisition of PRP involves key steps such as anticoagulated blood collection, centrifugal separation, and plasma collection.[24] Currently, preparation methods exhibit diverse characteristics, with core differences reflected in the selection of anticoagulants, setting of centrifugation parameters, and plasma separation techniques. Commonly used anticoagulants include sodium citrate or heparin. The former has minimal impact on platelet activation, while the latter may alter the release pattern of growth factors due to platelet activation.[25] The centrifugation process typically employs a two-step or single-step method: the two-step method separates red blood cells from the upper plasma through low-speed centrifugation, followed by high-speed centrifugation to concentrate platelets; the single-step method completes platelet enrichment through one centrifugation, which is more convenient but more difficult to control the concentration. The setting of centrifugation speed and time directly affects platelet recovery rate and activation status.[26] The common centrifugation parameter range in different studies is 1500–3000 revolutions per minute for 10–20 minutes, resulting in significant fluctuations in platelet concentration in the prepared PRP. Plasma separation techniques are divided into closed-tube systems (such as special PRP preparation kits) and open systems. The closed-tube system can reduce the risk of contamination and better meet aseptic requirements, while the open system is flexible in operation but difficult in quality control.[27]

PRP currently faces significant challenges across multiple medical fields, primarily due to the lack of standardization and therapeutic efficacy controversies triggered by compositional heterogeneity. Existing studies universally indicate notable variability in PRP preparation protocols, including differences in centrifugation methods, platelet concentration thresholds, and activation strategies.[28] These variations lead to heterogeneity in growth factor release kinetics and bioactive molecular profiles across studies, thereby affecting treatment outcomes. Meanwhile, commercial kits exhibit substantial discrepancies in centrifugation parameters and separation principles, resulting in highly inconsistent platelet concentrations and leukocyte contamination in final products.[29] Additionally, the selection of activators further exacerbates the comparability barriers of clinical outcomes. Therefore, establishing clinical indication-specific PRP preparation consensus, defining compositional quality control indicators (eg, platelet/leukocyte ratio, key growth factor

concentrations), and optimizing delivery strategies (eg, scaffold-based sustained release technology) have become urgent needs to promote PRP's transformation from an experimental therapy to a standardized treatment.[30]

Biological Activity Regulatory Mechanisms of PRP in the Treatment of Chronic Musculoskeletal Pain

Molecular Network Regulation in Tissue Repair

PRP has emerged as a promising therapeutic strategy in tissue repair and regeneration, leveraging its multifaceted mechanisms of action.[31] PRP delivers supraphysiological concentrations of growth factors (GFs), including PDGF, TGF-β, VEGF, and insulin-like growth factor-1 (IGF-1), which orchestrate the inflammatory, proliferative, and remodeling phases of tissue healing.[32] These GFs stimulate cellular proliferation, angiogenesis, and extracellular matrix synthesis through paracrine signaling, while platelet-released serotonin exhibits analgesic effects, modulating pain perception during tissue repair.[33]

PRP's immunomodulatory properties are mediated by leukocyte subpopulations, including neutrophils, monocytes, and lymphocytes, which regulate innate and adaptive immune responses.[34] Neutrophils promote pathogen clearance via neutrophil extracellular traps (NETs), while monocytes differentiate into anti-inflammatory M2 macrophages that suppress fibrosis and enhance tissue remodeling.[35,36] Additionally, PRP modulates satellite cell activation and myogenic differentiation in skeletal muscle repair, supported by interactions with fibro-adipogenic progenitors (FAPs) and endothelial cells to restore vascularization.[37] Notably, PRP's fibrin matrix acts as a scaffold for cell migration and GF retention, while platelet-derived factors inhibit TGF-β/Smad3 signaling to mitigate excessive collagen deposition.[38] Collectively, PRP's multifactorial actions—spanning GF delivery, immune regulation, and microenvironment modulation—underscore its therapeutic potential in tissue regeneration.[39]

PRP's ability to deliver concentrated growth factors and modulate inflammatory cascades makes it a promising intervention for chronic musculoskeletal pain, where dysregulated healing and persistent inflammation are key contributors.[40] By promoting tissue regeneration and reducing fibrosis, PRP may address the underlying pathophysiology of conditions like tendinopathy and myofascial pain syndromes. Furthermore, its analgesic effects via serotonin and anti-inflammatory cytokines could provide sustained pain relief in degenerative joint and muscle disorders.

Inflammation-Immune Microenvironment Modulation by PRP

PRP dynamically regulates the inflammation-immune microenvironment by modulating both innate and adaptive immune responses. Following tissue injury, PRP-derived growth factors and cytokines influence macrophage polarization, shifting the balance from pro-inflammatory M1 to anti-inflammatory M2 phenotypes to promote tissue repair while mitigating excessive inflammation.[41,42] Platelet-secreted serotonin further modulates immune cell activity by enhancing monocyte differentiation into dendritic cells and suppressing neutrophil overactivation.[43] PRP facilitates crosstalk between platelets and leukocytes via platelet surface receptors, which interact with immune cells to regulate NF-κB signaling, reducing oxidative stress and cytokine storms.[44] Additionally, PRP enhances T-cell-mediated adaptive immunity by promoting Th2 responses that support tissue regeneration while suppressing excessive Th1/Th17-driven inflammation.[45] The fibrin matrix stabilizes the healing niche by sequestering inflammatory mediators and providing a scaffold for immune cell migration, collectively orchestrating a balanced immune response to accelerate inflammation resolution and foster regenerative microenvironments.[46,47] The immunomodulatory properties of PRP are particularly relevant in chronic musculoskeletal pain, where prolonged M1 macrophage dominance and oxidative stress perpetuate tissue damage and nociceptive signaling.[48] By polarizing macrophages toward the M2 phenotype and dampening cytokine storms, PRP may break the cycle of inflammation-driven pain in conditions such as osteoarthritis and chronic tendinopathy. This dual role in immune regulation and inflammation resolution positions PRP as a viable strategy for managing pain in degenerative and overuse injuries.

Tissue-Specific Regulatory Mechanisms of PRP in Repair and Regeneration

PRP exhibits distinct regulatory mechanisms across tissues, reflecting its adaptability to specific regenerative microenvironments. In skeletal muscle repair, PRP enhances satellite cell activation and myogenic differentiation via growth factors (eg, IGF-1, HGF) and suppresses TGF-β-mediated fibrosis through VEGF-A/VEGFR-1 signaling, while promoting M2 macrophage polarization to reduce chronic inflammation and facilitate muscle fiber regeneration.[33] For tendon and ligament healing, PRP modulates collagen synthesis by balancing TGF-β and PDGF activity, favoring type III collagen deposition in early phases and enhancing type I collagen maturation in later stages.[49,50] In cartilage and osteochondral repair, high concentrations of TGF-β3 and BMPs in PRP stimulate chondrocyte proliferation and extracellular matrix production, while leukocyte-rich PRP (LR-PRP) may exert anti-inflammatory effects in osteoarthritis by inhibiting IL-1β and MMPs.[51–53] During cutaneous wound healing, PRP accelerates re-epithelialization via keratinocyte proliferation driven by EGF and VEGF, with its fibrin matrix supporting fibroblast migration and angiogenesis.[34] In nerve regeneration, PRP enhances Schwann cell activity and axonal regrowth through neurotrophic factors (eg, NGF, BDNF). These tissue-specific responses highlight PRP's versatility, with biological effects finely tuned by local cellular interactions and GF composition.[54,55]

Multidimensional Challenges in Translating PRP to Clinical Practice

Standardization Challenges and Quality Control Dilemmas in Preparation

The heterogeneity of PRP products caused by diverse preparation protocols has emerged as the primary bottleneck in clinical translation.[56] Current preparation parameters lack unified standards: centrifugation speeds vary between 1500–3000 rpm, while differences in centrifugation duration and anticoagulant selection significantly impact platelet activation states.[57] Commercially available PRP preparation kits employ divergent technological principles—some utilize density gradient centrifugation to enhance purity, while others rely on automated plasma separation systems. However, the resulting platelet concentrations range widely from 500,000 to 1,500,000/μL, with growth factor release variations exceeding 40%.[58]

Additional challenges include the absence of universally accepted quality control benchmarks for platelet viability, leukocyte contamination, and fibrinogen content, which further contribute to inter-product variability.[49] The lack of standardized protocols complicates comparative efficacy studies and raises concerns regarding reproducibility in clinical settings. The document emphasizes that 40% of diabetic foot ulcer trials show negative outcomes (Ajay et al, 2021) due to unregulated preparation methods.[59] A 2024 meta-analysis (Peng et al) confirmed this instability.[60]

Future efforts should focus on establishing consensus guidelines for centrifugation parameters, anticoagulant use, and platelet concentration thresholds, alongside rigorous quality control measures to ensure batch-to-batch consistency. Addressing these standardization and quality control dilemmas is essential for optimizing PRP therapeutic outcomes and facilitating regulatory approval.

Absence of Personalized Efficacy Prediction Models

The lack of precise efficacy prediction tools has confined PRP therapy to the realm of "empirical medicine." Research by Jarosz et al demonstrated that TGFB1 gene polymorphisms (eg, rs2278422 CC genotype) correlate significantly with pain relief, yet current clinical decision-making fails to incorporate genetic testing.[61] Ultrasound-based OMERACT scores (eg, synovitis grading) only predict short-term (2-month) functional improvements and cannot explain long-term outcome disparities.[62] Moreover, the biomarker system remains underdeveloped, and multi-omics technologies are still in their infancy, far from clinical application.

Methodological Flaws in Clinical Research Evidence Systems

Existing clinical evidence remains insufficient to robustly support the widespread use of PRP. Systematic reviews indicate variable success rates across musculoskeletal conditions: for instance, PRP demonstrates approximately 60–80% efficacy in knee osteoarthritis and tendinopathies over short-term follow-up, though long-term outcomes beyond one year remain inconsistently reported.[63–65] A 2023 system review reveals that most RCTs involve fewer than 50

participants, with a median follow-up duration too short to provide robust long-term efficacy data.[66] Study design limitations often introduce substantial bias. Furthermore, inconsistent outcome measures hinder evidence synthesis: pain assessments simultaneously employ VAS, NRS, FPS-R, and other scales, while functional evaluations utilize over 20 distinct tools (eg, WOMAC, VISA-P, Constant-Murley), making cross-study comparisons challenging.[67,68] Endpoint variability persists—minimal clinically important differences (MCID) for scales like VAS, PRTEE, and DASH are inconsistently defined.[69]

Obstacles to the Connection Between Ethical Regulation and Clinical Practice

The ethical challenges surrounding the clinical application of platelet-rich plasma (PRP) are becoming increasingly prominent, primarily manifested in the disconnect between evidence and practice, inadequate informed consent, and excessive use driven by commercial interests.[70] Although PRP has demonstrated potential in treating chronic musculoskeletal pain, many clinicians promote its use despite the lack of high-quality evidence-based medical support.[71] This may lead patients to undergo treatments with uncertain efficacy due to the "placebo effect" or misleading claims. The issue is particularly acute in professional sports, where athletes and agents, driven by the demand for rapid recovery, may push for the overuse of PRP.[72,73] Meanwhile, commercial entities often exaggerate its therapeutic benefits, further exacerbating ethical concerns in medical practice.

Additionally, the high cost of PRP therapy, coupled with its uncertain efficacy, creates a dilemma. Some patients may be unable to make fully informed decisions due to financial burdens or information asymmetry.[74] Moreover, the lack of standardized protocols and regulatory oversight allows for inconsistent clinical practices, raising questions about patient safety and equitable access to care.

Standardized PRP Preparation and the Outlook for Multi-Omics-Driven Precision Therapy Strategies

Prospects for Standardized Preparation

The clinical translation of PRP therapies has been hindered by significant heterogeneity in preparation protocols, leading to inconsistent therapeutic outcomes. To address this challenge, future efforts must prioritize the establishment of consensus-based guidelines that standardize critical parameters, including centrifugation speed, duration, and anticoagulant selection.[75] Additionally, rigorous quality control measures should be implemented to define acceptable thresholds for platelet concentration, leukocyte contamination, and fibrinogen content, ensuring batch-to-batch consistency. Commercially available PRP kits should undergo validation against these benchmarks, with regulatory agencies enforcing standardized manufacturing practices.[56] Furthermore, large-scale, multicenter clinical trials using harmonized PRP preparations will be essential to establish reliable efficacy correlations.[76] Such standardization will not only improve clinical outcomes but also facilitate regulatory approval and broader adoption of PRP therapies across medical specialties.[77]

Multi-Omics-Guided Precision Treatment Strategies for PRP Therapy

Genomics plays a pivotal role in advancing personalized applications of PRP therapy by investigating an individual's genetic blueprint.[57] This includes analyzing single nucleotide polymorphisms (SNPs), gene expression profiles, and epigenetic modifications, which collectively influence platelet functionality and tissue regeneration capacity. For instance, variations in genes encoding growth factors like TGF-β, PDGF, or VEGF may determine platelet activation thresholds or growth factor release kinetics.[78] The previous research underscores that PRP's efficacy relies on these bioactive molecules to stimulate collagen synthesis and angiogenesis.[79] Genomic profiling can identify patients with polymorphisms that enhance or impair these pathways, enabling stratification of responders versus non-responders. Additionally, epigenetic markers may reveal how environmental factors modulate PRP responsiveness.[80] By integrating genomic data with PRP's mechanisms clinicians can tailor protocols to optimize outcomes.[81]

Proteomics provides a powerful tool for evaluating the therapeutic potential of PRP by systematically analyzing protein expression patterns, particularly growth factors such as TGF-β, VEGF, and PDGF, which are critical for tissue repair and regeneration.[82] Study demonstrates that CD226 deficiency in platelets leads to impaired α-granule secretion,

reducing PDGF-AB levels by 47% and significantly diminishing PRP efficacy in osteoarthritis treatment, as evidenced by a 2.3-fold increase in OARSI scores. iTRAQ-based proteomic analysis identified 170 differentially expressed proteins, with 119 downregulated, including autophagy-related markers Beclin1 and LC3-II, which correlate with defective platelet maturation.[83] In the future biomarker signatures, including platelet maturation markers (CD226, Beclin1) and α-granule secretion profiles, may predict treatment responsiveness. Integrating proteomic data with clinical parameters could optimize PRP formulations and personalize therapy for enhanced pain relief and tissue regeneration.

Metabolomics focuses on metabolic composition and pathways, including those related to energy metabolism, inflammatory responses, and tissue repair. PRP's metabolic effects may significantly influence regenerative processes.[84] Metabolomic analysis can evaluate PRP's impact on metabolic pathways, refining treatment strategies. Furthermore, metabolomics helps identify metabolic biomarkers linked to PRP efficacy, enhancing individualized therapy.[85]

Multi-omics integration combines genomic, proteomic, and metabolomic data to comprehensively assess a patient's biological profile. By cross-referencing genetic polymorphisms with proteomic signatures and metabolic dysregulation, clinicians can stratify patients into distinct responder subgroups and customize PRP formulations accordingly.[78,86] This holistic approach enables optimized PRP formulation and dosing. For instance, integrating genomic and proteomic data can identify high-responders and tailor more effective treatment plans. This systems biology approach not only refines PRP efficacy but also mitigates trial-and-error inefficiencies, paving the way for standardized yet personalized regenerative medicine.

To maximize the therapeutic potential of platelet-rich plasma, researchers must pursue several key avenues. First, integrating multi-omics data through advanced computational approaches could enable more comprehensive patient characterization, potentially revealing novel biomarkers for treatment response. Second, the development of personalized PRP protocols tailored to individual patients' molecular profiles may significantly enhance treatment precision and clinical outcomes. Third, rigorous long-term studies are needed to systematically evaluate both the sustained benefits and potential safety concerns associated with PRP interventions across different clinical applications. Together, these efforts could transform PRP from an empirically-used therapy into a precisely tailored treatment modality grounded in robust scientific evidence. In summary, these efforts could transform PRP into a precisely tailored treatment modality for chronic pain, grounded in robust scientific evidence.

Conclusion

In conclusion, PRP therapy offers a biologically plausible strategy for managing chronic musculoskeletal pain through its roles in growth factor delivery, immunomodulation, and tissue regeneration. Nevertheless, its clinical application faces significant hurdles, including lack of standardization in preparation, absence of validated efficacy-prediction models, methodological limitations in clinical studies, and ethical concerns related to evidence-practice gaps. Moving forward, concerted efforts must focus on establishing standardized preparation protocols, advancing multi-omics-guided personalized treatment strategies, and conducting rigorously designed long-term clinical trials. Interdisciplinary collaboration among scientists, clinicians, and regulators will be crucial to realizing the full therapeutic potential of PRP and ensuring its ethical and effective integration into chronic pain management protocols.

Data Sharing Statement

The datasets used during the present study are available from the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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