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Advances in Complex Tissue Regeneration Using Adipose-Derived Stem Cells, Platelet-Rich Plasma, and Biomaterials: Mechanisms, Clinical Evidence, and Translational Perspectives

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Abstract*—Recent advancements in tissue engineering have been directed toward the integration of adipose-derived stem cells (ADSCs), platelet-rich plasma (PRP), and biomaterial scaffolds to facilitate the regeneration of structurally and functionally complex tissues. This approach has been investigated due to the individual and synergistic regenerative properties exhibited by these biological components. Their combined application has been explored extensively in the restoration of orthopaedic, maxillofacial, dermatological, and cardiovascular tissues, where conventional therapies often remain insufficient. The primary objective of this review was to examine the current evidence supporting the use of ADSCs, PRP, and biomaterials in complex tissue engineering and to elucidate their mechanisms of action, therapeutic potential, and translational viability. Relevant literature was identified through a non-systematic search of peer-reviewed publications in databases including PubMed, Scopus, and Web of Science, with emphasis placed on preclinical and clinical studies published in the last decade. Studies focusing exclusively on one component without integration into a tissue engineering framework were excluded. Key findings indicate that ADSCs contribute to tissue regeneration through multipotent differentiation and paracrine signaling, while PRP enhances cellular proliferation and neovascularization via growth factor release. Biomaterial scaffolds have been engineered to provide structural support, regulate degradation kinetics, and promote cell-matrix interactions. When used in combination, these elements have demonstrated enhanced outcomes in bone, cartilage, skin, and myocardial tissue models. It is concluded that the synergistic application of ADSCs, PRP, and biomaterials represents a promising therapeutic paradigm. Future research is warranted to optimize delivery strategies, standardize protocols, and validate long-term efficacy in large-scale clinical trials.*

***Keywords*—** *Adipose-derived stem cells; Platelet-rich plasma; Biomaterials; Tissue engineering.*

I. Introduction

Complex tissue damage, often involving multi-cellular degradation, vascular disruption, and extracellular matrix (ECM) disorganization, has been identified as a persistent challenge in the field of regenerative medicine. Traditional treatment modalities, including autografts, allografts, and synthetic prostheses, have frequently been associated with limited integration, donor site morbidity, and suboptimal restoration of native tissue function. As a result, the need for biologically inspired, functionally integrative strategies has been increasingly recognized.

To address these limitations, a multi-component approach incorporating stem cells, autologous growth factors, and biocompatible scaffolds has been widely adopted. Among various stem cell sources, adipose-derived stem cells (ADSCs) have been preferentially utilized due to their abundance, ease of isolation through minimally invasive procedures, and capacity for multilineage differentiation (1). When used in conjunction with platelet-rich plasma (PRP) and advanced biomaterial scaffolds, ADSCs have demonstrated enhanced regenerative efficacy in numerous preclinical and clinical studies (2–4). These integrated systems have shown promising results in the regeneration of bone, cartilage, dermal, and myocardial tissues, each characterized by complex structural and functional requirements (5–8).

II. Mechanism of Action / Basic Science

The biological basis for the combined use of ADSCs, PRP, and biomaterials in tissue engineering lies in the interplay between stem cell differentiation, paracrine signaling, and scaffold-guided tissue remodeling.

2.1 Adipose-Derived Stem Cells (ADSCs)

ADSCs exert their regenerative effect through two primary mechanisms: multilineage differentiation and paracrine secretion. Upon implantation, ADSCs differentiate into target cell types (e.g., osteoblasts, chondrocytes, fibroblasts) guided by local cues and scaffold composition (1,4). Concurrently, they secrete trophic factors such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β), and hepatocyte growth factor (HGF), which promote angiogenesis, suppress inflammation, and recruit host progenitor cells (9).

2.2 Platelet-Rich Plasma (PRP)

PRP functions as a biologically active reservoir rich in growth factors and cytokines. Upon activation, platelet α-granules release platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and VEGF, which collectively modulate cell proliferation, gene expression, and matrix remodeling (2,3).

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PRP has also been shown to enhance chondrogenic and osteogenic differentiation of ADSCs by upregulating lineage-specific gene expression (6,7,10).

2.3 Biomaterials and Scaffold Interaction

Biomaterials provide the structural support and biochemical cues necessary for cell attachment, migration, and organization. The scaffold's porosity, mechanical properties, and degradation rate significantly influence mechanotransduction and cellular behavior (11). Furthermore, scaffold surface modification using peptides or ECM analogs has been shown to enhance cellular integration and regenerative potential (12).

Collectively, the triad of ADSCs, PRP, and engineered scaffolds orchestrates a harmonized regenerative response through cellular regeneration, angiogenesis, and matrix remodeling (1–12).

III. Device/Technique/Intervention Overview

3.1 Adipose-Derived Stem Cells (ADSCs)

ADSCs are typically isolated via tumescent liposuction, followed by enzymatic digestion with collagenase, and subsequent centrifugation and culture expansion under sterile conditions. The identity and quality of these cells are validated through flow cytometry by detecting surface markers such as CD73, CD90, and CD105, and confirming the absence of hematopoietic markers like CD34 and CD45 (13). Depending on the application, ADSCs may be directly injected into damaged tissue or seeded onto biomaterial scaffolds for pre-cultured implantation strategies.

3.2 Platelet-Rich Plasma (PRP)

PRP is prepared through differential centrifugation of autologous blood, resulting in a platelet-enriched fraction that may be either leukocyte-rich (LR-PRP) or leukocyte-poor (LP-PRP) depending on the protocol used (14). Before clinical application, PRP is often activated with calcium chloride or thrombin, which triggers platelet degranulation and the release of growth factors such as PDGF, TGF-β1, VEGF, and IGF, critical for modulating cell proliferation, inflammation, and matrix remodeling. When mixed with ADSCs, PRP has demonstrated improved regenerative potential in both preclinical and clinical applications (14).

3.3 Biomaterial Scaffolds

Scaffolds serve as the structural and biochemical platform for tissue regeneration. Commonly used natural biomaterials include collagen, fibrin, and gelatin, while synthetic options such as polycaprolactone (PCL), polylactic acid (PLA), and PLGA offer tunable degradation rates and mechanical properties. Fabrication methods such as electrospinning, freeze-drying, and 3D bioprinting allow control over porosity and topography to support cell infiltration and nutrient exchange (15). Injectable hydrogels incorporating PRP and ADSCs have been explored for minimally invasive tissue engineering, particularly in irregular or difficult-to-access defects (15).

The combination of ADSCs, PRP, and biomaterials has enabled both pre-fabricated implants and in situ-formed regenerative constructs, offering therapeutic versatility across orthopedic, dermatologic, and cardiac applications (16).

IV. Clinical Evidence

4.1 In Vitro Studies

Multiple in vitro studies have demonstrated that PRP-conditioned media enhances the osteogenic and chondrogenic differentiation of ADSCs by upregulating lineage-specific transcription factors such as Runx2 and Sox9 (16). PRP also improves the proliferation and extracellular matrix (ECM) secretion capacities of ADSCs in both monolayer and 3D scaffold cultures.

4.2 Animal Models

In a rat calvarial defect model, scaffolds composed of polycaprolactone loaded with ADSCs and PRP led to significantly increased bone volume and angiogenesis compared to controls (13). Similarly, in rabbit osteochondral defect models, fibrin matrices seeded with PRP-preconditioned ADSCs demonstrated superior cartilage regeneration, including enhanced GAG content and collagen II expression (15). In a porcine full-thickness wound model, dermal regeneration was accelerated using ADSC-PRP constructs, with observed improvements in wound closure rate, vascularization, and collagen fiber alignment (17).

4.3 Clinical Trials

In orthopedic interventions, such as rotator cuff repair and knee cartilage lesions, intraoperative application of autologous ADSC-PRP constructs has resulted in reduced inflammation and accelerated tissue healing, as supported by MRI and functional outcome scores (16). In dermatology, particularly in the treatment of chronic ulcers and deep burns, the co-application of PRP and ADSCs led to rapid re-epithelialization, improved vascular density, and decreased fibrotic remodeling (17). Early-phase cardiology trials investigating the injection of ADSC-PRP hydrogels into infarcted myocardium have shown improvements in ejection fraction, reduced scar volume, and enhanced left ventricular wall thickness, supporting the therapeutic potential in myocardial regeneration (18).

Study	Tissue Type	Intervention	Outcome
Andia et al., 2018	Cartilage	ADSC + PRP in collagen gel	Improved ICRS scores, MRI regeneration
Gentile et al., 2017	Skin	PRP + ADSC gel	Accelerated epithelialization, less pain
Alt et al., 2020	Myocardium	ADSC + PRP injectable gel	↑ LVEF, ↓ infarct size

V. Regulatory & Commercial Status

5.1 Adipose-Derived Stem Cells (ADSCs)

ADSCs are regulated under the “minimal manipulation” clauses in many jurisdictions; for example, in the U.S., they fall under the FDA’s Investigational New Drug (IND)

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pathway unless used autologously during same-day surgical procedures (18,27). In Europe, they are classified as Advanced Therapy Medicinal Products (ATMPs) and require centralized approval before clinical use (29).

5.2 Platelet-Rich Plasma (PRP)

PRP is generally categorized as a minimally manipulated autologous biologic, which allows for broad off-label use in orthopedics, dermatology, and plastic surgery without formal drug or device classification (18,26). While its use is widespread, regulatory standardization is lacking across regions, which contributes to variability in clinical outcomes (28).

5.3 Biomaterial Scaffolds

Scaffolds composed of collagen, PLA, PCL, and related polymers are CE-marked or FDA-cleared based on their intended use, such as for bone void filling or chronic wound management (23,25). However, once these biomaterials are combined with living cells (e.g., ADSCs), they are classified as combination products and require additional regulatory oversight under both device and biologic frameworks (24). In India, collagen matrices and PRP kits have received DCGI approval, whereas clinical use of ADSCs remains under review by the Indian Council of Medical Research (ICMR) guidelines (30).

VI. Comparative Analysis

When compared with bone marrow-derived mesenchymal stem cells (BM-MSCs), ADSCs exhibit higher proliferative capacity and easier harvest procedures, while maintaining comparable multilineage potential (21,31). In addition, PRP has been shown to activate ADSCs more effectively than fetal bovine serum (FBS) when used as a supplement in in vitro culture media (20,25).

From a biomaterials perspective, natural polymers such as collagen offer superior biocompatibility and cell adhesion, yet often lack mechanical strength, making them less suitable for load-bearing applications (23). Conversely, synthetic polymers like PCL and PLGA provide tunable degradation kinetics and enhanced mechanical performance, although surface modification (e.g., ECM coatings) is often required to improve cell affinity (22,28).

Clinical studies comparing ADSC + PRP composites with PRP alone consistently demonstrate superior long-term integration and functional recovery, particularly in orthopedic and soft tissue repair settings (19,27,32).

VII. Limitations, Controversies, and Challenges

Despite encouraging preclinical and clinical data, multiple challenges hinder the broad application of ADSC-PRP-biomaterial therapies. One key limitation lies in the variability of PRP preparation protocols, which can significantly alter growth factor content and therapeutic outcomes (18,20). Furthermore, ADSC populations are inherently heterogeneous, and their regenerative potential is influenced by donor age, metabolic status, and comorbidities (30,31).

Another major concern is the lack of standardized scaffold fabrication and cell-seeding methods, which limits comparability between studies and impedes clinical translation (22,24). Regulatory ambiguity—especially in combination products involving live cells and bioactive matrices—further delays market clearance and clinical accessibility (29).

A notable controversy involves the oncological safety of ADSCs, particularly in post-cancer reconstruction or chronic inflammation settings, where paracrine activity might inadvertently support tumorigenesis or angiogenesis (33,34). In the absence of definitive long-term safety data, clinical use of ADSCs in oncology-related wounds remains under caution (33).

VIII. Future Perspectives

The next wave of regenerative medicine is expected to be shaped by the convergence of nanotechnology, gene editing tools like CRISPR-Cas9, and AI-based predictive modeling, which aim to enhance scaffold precision, guide stem cell behavior, and optimize personalized therapies (23,34). Smart biomaterials responsive to mechanical stress or biochemical gradients are already being engineered to provide real-time microenvironment modulation, enhancing integration and functional regeneration (21,22).

Integrating ADSC-based systems into personalized medicine platforms, supported by telemedicine diagnostics and AI-powered outcome tracking, is also being explored to improve treatment precision and scalability (30,34). Nonetheless, substantial research gaps persist—most notably, the absence of uniform PRP protocols, cell characterization standards, and long-term efficacy/safety data across diverse patient populations (19,31).

Progress in this field will rely heavily on large-scale, randomized clinical trials, and the development of clear regulatory guidelines to support global adoption (18,29).

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