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Characterization of Anterior Cruciate Ligament–Derived Stem Cells (ACL-DSCs) in Anterior Cruciate Ligament Rupture: A Literature Review

Erick Yudistira Christanto, M.D.[1,2], Dwikora Novembri Utomo, M.D., Ph.D. .[1,2]*, Andre Triadi Desnantyo, M.D. .[1,2]

[1]Department of Orthopedics and Traumatology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia
[2]Department of Orthopedics and Traumatology, Dr. Soetomo General Academic Hospital, Surabaya Indonesia

***Corresponding Author**
Dwikora Novembri Utomo, M.D., Ph.D.
Department of Orthopaedics and Traumatology, Faculty of Medicine, Universitas Airlangga, Dr. Soetomo Regional General Hospital, Surabaya 60286, Indonesia
dwikora-novembri-u@fk.unair.ac.id

ABSTRACT

This review synthesizes current evidence on anterior cruciate ligament–derived stem/stromal cells (ACL-DSCs) as a potential autologous cell source for ligament regeneration. Narrative analysis of in vitro, animal, and early clinical studies highlights their consistent mesenchymal immunophenotype and a tissue-specific bias toward ligament lineage, with higher expression of master regulators such as SCX and MKX compared with bone marrow derived MSCs. Under tenogenic cues, ACL-DSCs demonstrate enhanced proliferation, extracellular matrix deposition, and secretion of trophic mediators, including IGF-1, that promote fibroblast proliferation, collagen synthesis, angiogenesis, and enthesis maturation. Collagen-based and biomimetic scaffolds further augment their regenerative potential, supporting ligament-like matrix formation and tendon-to-bone integration. Preclinical models report accelerated graft ligamentization and improved biomechanical outcomes, although translational progress remains constrained by heterogeneity in isolation and induction protocols, variability in outcome measures, limited human data, and undefined dosing or delivery strategies. ACL-DSCs therefore represent a promising, tissue-matched candidate for biologically informed ACL reconstruction, but standardization of protocols, harmonization of imaging and histologic endpoints, and adequately powered clinical trials are required to establish efficacy, safety, and long-term durability.

KEYWORDS: ACL-derived stem cells, anterior cruciate ligament, ligament regeneration, mesenchymal stem cells, tissue engineering.

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INTRODUCTION

The management of musculoskeletal tissue injuries and their subsequent regeneration continues to represent a major challenge in contemporary medicine. Among the key structures involved, the anterior cruciate ligament (ACL) is of particular importance due to its essential role in maintaining knee joint stability by anchoring the femur to the tibia. Rupture of the ACL remains a clinically significant problem, particularly within athletic and physically active populations, as the tissue possesses limited intrinsic regenerative capacity and requires prolonged rehabilitation. Epidemiological data indicate that more than 30 million tendon and ligament injuries occur annually worldwide, with the incidence of ACL rupture estimated at approximately 37 per 100,000 individuals, and the prevalence rising markedly among professional athletes [1–6] Beyond the immediate functional impairment, ACL rupture is associated with an elevated risk of secondary meniscal injury and the accelerated onset of post-traumatic knee osteoarthritis, which collectively contribute to long-term disability [2,7–11]

The spontaneous healing capacity of the ACL is severely constrained by the unfavorable intra-articular environment. The absence of a stabilizing fibrin–platelet clot, largely due to the continuous circulation of synovial fluid and elevated plasmin levels, prevents the formation of an adequate scaffold for repair. Consequently, healing typically results in fibrotic scar tissue rather than functional ligament tissue, leading to reduced biomechanical performance [7,8,10,12–17] A wide range of surgical strategies have been investigated, including primary ligament repair, autografts, allografts, xenografts, and prosthetic substitutes [13,18–22] However, none of these approaches have consistently achieved optimal outcomes. Reconstruction using autologous tendon grafts remains the current gold standard, yet it is invasive and accompanied by donor-site morbidity, immune reactions, graft necrosis, and extended recovery periods, all of which limit its overall effectiveness (Butler, Juncosa, and Dressler, 2004).

In light of these persistent limitations, cell-based regenerative strategies have gained considerable interest as alternative therapeutic options. Mesenchymal stem/stromal cells (MSCs), first characterized by Caplan (1991), exhibit high proliferative capacity, multilineage differentiation potential, and notable immunomodulatory effects. MSCs can be harvested from diverse tissue sources, including bone marrow, adipose tissue, periosteum, and synovial membrane [18,19,23–29] Their application in ligament tissue engineering has continued to expand over the past decades. Moreover, multiple growth factors such as transforming growth factor-β (TGF-β), insulin-like growth factors (IGF-1/2), vascular endothelial growth factor (VEGF), platelet-derived growth

factor (PDGF), and basic fibroblast growth factor (bFGF) play crucial roles in ligament healing by modulating fibroblast proliferation, angiogenesis, and extracellular matrix remodeling. Among these, IGF-1 is particularly relevant, as it stimulates fibroblast proliferation and collagen synthesis during the early phases of repair, with experimental studies further demonstrating its positive effect on the mechanical strength of injured ligaments [30–36].

In addition to soluble growth factors, scaffolds provide an indispensable structural and biochemical microenvironment for ligament regeneration. The extracellular matrix (ECM) of ligaments is rich in fibrillar proteins and bioactive cues that direct ligament-specific cell differentiation. Researchers demonstrated that transplantation of ligament-derived stem/progenitor cells (TSPCs) into decellularized ligament ECM enhanced cell proliferation and induced lineage-specific differentiation. Importantly, MSCs exert their reparative effects not only through direct differentiation but also via their secretome, which comprises a complex array of cytokines, growth factors, and regulatory molecules that act in a paracrine manner to support tissue repair [30–32,35,37–42] Within this evolving field, increasing attention has been directed toward anterior cruciate ligament–derived stem/stromal cells (ACL-DSCs), which are isolated directly from ACL tissue. These cells demonstrate characteristic mesenchymal immunophenotypes, including expression of CD73 and CD90, and exhibit an inherent commitment toward ligamentous lineage, as evidenced by the upregulation of key transcription factors such as Scleraxis (SCX) and Mohawk (MKX) [43]. Compared with bone marrow–derived MSCs (BM-MSCs), ACL-DSCs have demonstrated superior ligamentogenic potential, positioning them as a highly relevant candidate for ACL regeneration.

Against this background, systematic characterization of ACL-DSCs and their ligamentogenic potential is essential to clarify their role as a promising autologous cell source for regenerative ACL reconstruction. Synthesizing the available evidence regarding their biomarker expression, lineage specificity, and regenerative profile will provide critical insights into their translational potential and inform the development of clinically applicable strategies for musculoskeletal tissue engineering.

Mesenchymal stem/stromal cells (MSCs) are adult multipotent progenitors capable of extensive self-renewal and differentiation into a wide spectrum of mesenchymal lineages, including osteogenic, chondrogenic, adipogenic, myogenic, tendinous, and ligamentous phenotypes. In addition to this lineage plasticity, MSCs exert potent trophic and immunomodulatory effects through a complex secretome comprising cytokines, chemokines, and growth factors. These paracrine mediators orchestrate the resolution of inflammation, stimulate angiogenesis, regulate extracellular matrix remodeling, and ultimately establish a microenvironment conducive to tissue repair and regeneration [44,45] MSCs can be harvested from a range of tissue sources, each possessing distinct biological and practical advantages. Bone marrow–derived MSCs (BM-MSCs) remain the most extensively investigated in orthopedic tissue engineering, demonstrating robust osteochondral potential and proven tenogenic plasticity under biochemical or mechanical induction. However, the harvesting of BM-MSCs is invasive, and their proliferative and differentiation capacities may decline with advancing age .

Mechanistically, the regenerative contribution of MSCs in ligament repair can be understood through three complementary pathways. First, MSCs can undergo direct differentiation into fibroblast-like effector cells that actively synthesize ligamentous extracellular matrix. Second, through their paracrine activity, MSCs stimulate resident fibroblasts, endothelial cells, and immune cells via the release of growth factors such as TGF-β, IGF-1/2, VEGF, PDGF, and bFGF, thereby enhancing proliferation, collagen synthesis, and angiogenesis. Third, MSCs exert immunomodulatory effects by attenuating excessive inflammation while simultaneously promoting constructive tissue remodeling, a dual action that is critical for the creation of a favorable healing environment [46–48]

Preclinical investigations in models of ACL injury and reconstruction have demonstrated that MSC delivery, either alone or in conjunction with pro-angiogenic stimuli, enhances graft ligamentization, accelerates tendon-to-bone integration, and improves biomechanical strength. Nonetheless, translation into consistent clinical outcomes remains challenging. Variability in cell source, seeding density, delivery routes, scaffold materials, and evaluation metrics has produced heterogeneous findings, underscoring the need for standardized protocols and rigorous clinical validation [45,49]

A defining hallmark of ACL-DSCs is their inherent tissue-specific priming toward the ligament lineage. Under identical tenogenic induction conditions, ACL-DSCs demonstrate higher expression levels of tendon/ligament master transcription factors particularly Scleraxis (SCX) and, in many cases, Mohawk (MKX) alongside increased expression of ligament-associated extracellular matrix genes when compared to BM-MSCs [43] This transcriptional advantage provides strong support for the “tissue memory” hypothesis, which postulates that progenitors derived from the tissue of origin retain an intrinsic predisposition to regenerate that specific tissue. Scaffold context has been shown to reinforce this bias: ACL-DSCs cultured on collagen-based matrices exhibit greater proliferation rates and enhanced ligament-like matrix deposition, underscoring the critical role of extracellular matrix cues in promoting lineage-appropriate differentiation [50–52]

From a translational perspective, ACL-DSCs present multiple pragmatic advantages relative to non–tissue-matched MSCs. First, autologous sourcing from ACL remnants circumvents the need for invasive bone marrow aspiration while minimizing risks of immunogenic rejection. Second, the inherent lineage alignment of ACL-DSCs can expedite or enhance graft ligamentization through the combined effects of direct differentiation (driven by SCX/MKX expression) and paracrine support (e.g., IGF-1–mediated fibroblast proliferation and collagen synthesis) [43,53]. Third, ACL-DSCs can act synergistically with biological scaffolds or remnant-preserving surgical techniques, both of which have been associated with reduced tunnel widening, more mature tendon-to-bone integration, and histological features resembling native ligament in preclinical and pilot clinical investigations, though reported clinical effect sizes remain variable [54,55]

Despite these advantages, several limitations temper current evidence. Variability in isolation techniques, culture conditions, mechanical stimulation regimens, and biomarker panels contributes to heterogeneity across studies, complicating direct comparisons and evidence synthesis [43,56] Moreover, although in vitro and animal models consistently support the ligamentogenic bias of ACL-DSCs, robust human clinical data remain scarce. Standardized endpoints for evaluating "biologic success" such as imaging biomarkers of ligamentization, quantitative assessments of tunnel remodeling, and detailed histologic grading of enthesis quality are still evolving [49,54,57].

CONCLUSION

Anterior cruciate ligament–derived stem cells (ACL-DSCs) are tissue-matched progenitors with strong ligamentogenic potential, characterized by upregulation of SCX and MKX, secretion of IGF-1, and responsiveness to collagen-based scaffolds. These properties distinguish them from bone marrow–derived MSCs and position them as promising candidates for biologically enhanced ACL reconstruction. Unlike conventional techniques that restore only mechanics, ACL-DSCs enable biological regeneration through structural and functional repair. To realize this potential, standardized protocols and well-designed clinical trials are required to confirm their safety, efficacy, and long-term outcomes.

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