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Research Article

Autologous Cardiac Stem Cell Therapy: Current Evidence, Mechanisms, and Emerging Directions

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Abstract

Cardiac regeneration remains an unmet clinical need, given the limited proliferative capacity of adult human cardiomyocytes. Stem-cell-based approaches have been intensively evaluated over the past two decades, with a major focus on autologous cell sources, including bone-marrow-derived mononuclear cells (BM-MNC), mesenchymal stromal/stem cells (MSCs), CD133$^+$ progenitors, adipose-derived progenitors, and cardiac-derived stem/progenitor cells (CPCs). While early enthusiasm regarding endogenous "cardiac stem cells" has been tempered by rigorous lineage-tracing studies disproving their cardiomyogenic potential, autologous cells continue to show paracrine-mediated benefits in remodelling, microvascular perfusion, and immune modulation. This review synthesizes current knowledge, examines clinical trial evidence, discusses the mechanistic basis of autologous therapy, and highlights emerging next-generation biologics including exosomes, engineered progenitors, and hydrogel-based delivery systems.

Introduction

Heart Failure (HF), driven predominantly by ischemic injury, cardiomyocyte loss, and maladaptive remodeling, remains a leading cause of morbidity and mortality worldwide [1]. These alarming statistics persist, despite substantial advances in pharmacologic and device-based therapies [2]. Autologous stem-cell therapy emerged in the early 2000s following influential preclinical studies showing improved ventricular function after transplantation of bone marrow-derived progenitors into infarcted myocardium, which catalyzed rapid translation into early-phase clinical trials [3-6]. The use of autologous cell products offers major translational advantages, including avoidance of alloimmune rejection, elimination of immunosuppression requirements, simplified donor compatibility, and feasible bedside-to-bench iteration in which patient-derived cells can be phenotyped and optimized in parallel with clinical deployment [7].

However, successive advances in developmental biology and genetic lineage tracing have overturned the concept of a self-renewing endogenous cardiac stem cell compartment capable of restoring cardiomyocyte mass. Rigorous fate-mapping studies demonstrated that adult c-Kit$^+$ cardiac cells contribute primarily to endothelial lineages and generate cardiomyocytes at physiologically negligible rates, while similar studies failed to support meaningful cardiomyogenic contribution from Sca-1$^+$ populations [8,9]. These findings have been consolidated in contemporary consensus reviews concluding that adult mammalian myocardium lacks a resident stem-cell pool with reparative cardiomyogenic capacity, shifting the therapeutic rationale for cell therapy from "remuscularization" to "biological modulation [10-12]."

Despite the absence of durable engraftment and cardiomyocyte replacement, autologous cell populations, including MSCs, bone marrow mononuclear cells (BM-MNCs), CD133$^+$ progenitors, and adipose-derived stromal/stem cells, continue to demonstrate

modest but reproducible benefits in carefully selected patient subsets [13,14]. Mechanistic studies increasingly indicate that observed improvements in ventricular remodeling and clinical outcomes are mediated predominantly through paracrine signaling, including secretion of angiogenic growth factors (e.g., VEGF, HGF), immunomodulatory cytokines (e.g., IL-10, TGF-β), and extracellular vesicles enriched in pro-repair microRNAs that collectively promote neovascularization, attenuate inflammation, suppress fibrosis, and enhance cardiomyocyte survival [15-17]. This evolving mechanistic understanding has motivated next-generation development toward exosome-based biologics, biomaterial-enabled retention strategies, and precision selection of high-potency autologous cell products guided by multi-omics and machine learning approaches.

Biological Basis for Autologous Cardiac Repair

The limited intrinsic regenerative capacity of the adult human heart represents the fundamental biological rationale for autologous cell-based therapeutic strategies. Quantitative radiocarbon analyses have demonstrated that adult human cardiomyocytes renew at a rate of only 0.5-1% per year, an order of magnitude too low to compensate for the ~1 billion cardiomyocytes lost after a typical myocardial infarction (MI) [18,19]. Following birth, mammalian cardiomyocytes rapidly exit the cell cycle, undergo polyploidization, and transition to hypertrophic growth, extinguishing the transient regenerative program that characterizes neonatal mammals [20,21]. Although early postnatal mice retain the capacity for complete cardiac regeneration for approximately seven days, this capacity disappears shortly thereafter, highlighting a narrow developmental window during which cardiomyocyte proliferation is possible [22,23].

For nearly two decades, enthusiasm surrounded the hypothesis that the adult heart contains a dedicated endogenous stem-cell reservoir capable of replenishing lost myocardium. Initial studies suggested that c-Kit$^+$ or Sca-1$^+$ cardiac-resident cells could differentiate into functional cardiomyocytes and thus serve as bona fide cardiac stem cells. However, these claims have been rigorously refuted. Using dual-recombinase and Cre-loxP-based lineage-tracing, [24]. demonstrated that c-Kit$^+$ cells contribute almost exclusively to endothelial populations, with negligible cardiomyogenic potential [24]. Similar investigations showed no physiologically meaningful contribution of Sca-1$^+$ populations to the cardiomyocyte lineage [25].

More broadly, comprehensive analyses of the adult myocardium have shown that no measurable stem cell compartment exists that can regenerate functional cardiomyocytes *in vivo* [26]. A recent review by Eschenhagen and Weinberger in 2021 [10] synthesized these findings, concluding that the notion of an adult cardiac stem cell capable of myocardial regeneration is biologically unsupported and inconsistent with contemporary genetic evidence. This conceptual shift is further reinforced by large scale reviews of pluripotent and adult cell based cardiac repair strategies, including [12]. which emphasize that paracrine signaling rather than cardiomyogenic differentiation underlies the therapeutic benefit observed in cell therapy studies. Earlier foundational perspective (exemplified in references [27,28],) also recognized the stark contrast between regenerative capacities in lower vertebrates (e.g., zebrafish and newt) and the modest, largely insufficient reparative mechanisms available in adult mammals. The analysis, along with subsequent lineage tracing studies, helped to dismantle the premise of endogenous cardiomyocyte regeneration through resident stem cells and shifted the therapeutic focus toward exogenous cell delivery, trophic support, and modulation of the injury milieu. Taken together, modern genetic, developmental, and physiological data converge on the principle that meaningful cardiac repair in adult humans cannot be achieved through endogenous cardiomyocyte regeneration. Instead, the rationale for autologous cell therapy rests on the capacity of transplanted cells, irrespective of lineage or differentiation stage, to deliver paracrine, immunomodulatory, angiogenic, and anti-fibrotic signals that favourably influence remodeling, survival, and ventricular function after injury. This biological framework forms the underpinning of next generation autologous cardiac repair strategies, including MSC- and CPC-based therapies, exosome therapeutics, and engineered cell matrix constructs.

Autologous Cell Sources for Cardiac Repair

Bone marrow mononuclear cells (BM-MNCs) represent the earliest and most extensively tested autologous cell population for cardiac repair, owing to their ease of isolation, rapid intra-procedural preparation, and established safety profile. Pivotal trials including REPAIR-AMI and BOOST demonstrated initial improvements in left ventricular ejection fraction (LVEF), yet these gains diminished over long-term follow-up, revealing limited durability of the effect [29-31]. Mechanistic studies have definitively shown that BM-MNCs do not transdifferentiate into cardiomyocytes, and beneficial outcomes arise almost exclusively from their paracrine activity, including secretion of angiogenic growth factors, immunomodulatory cytokines, and pro-survival mediators [32-34]. A 2024 synthesis of clinical trial data highlighted the overall modest functional benefit of BM-MNC therapy, with only minimal long-term LVEF improvement while maintaining a strong safety record across ischemic and nonischemic cardiomyopathy cohorts [15]. Despite the limited magnitude of efficacy, BM-MNCs laid the foundational framework for subsequent autologous cell-based therapeutics and continue to serve as an important comparator population in next generation trials.

Autologous mesenchymal stromal/stem cells (MSCs), derived from bone marrow, adipose tissue, or perinatal tissues, exhibit a more potent immunomodulatory and trophic secretome than BM-MNCs, positioning them as a leading therapeutic candidate for cardiac repair. MSCs exert robust anti-inflammatory, pro-angiogenic, anti-fibrotic, and pro-survival effects through the release of VEGF, HGF, IL-10, exosomes, and matrix remodeling enzymes [35-38]. Clinically, multiple Phase I/II trials have demonstrated that autologous MSC administration leads to improvements in ventricular remodeling, including reductions in LV end systolic volume and stabilization of myocardial structure [39,40]. Cardiac delivery efficiency remains a central obstacle, as

systemically infused MSCs demonstrate poor myocardial homing. Biomaterials based strategies have therefore emerged to enhance cell retention. A notable advance is the intrapericardial delivery of MSCs encapsulated within methacrylated hyaluronic acid (MA-HA) hydrogels, which improves local persistence, attenuates inflammation, enhances angiogenesis, and augments post-MI recovery [41]. Such approaches align with a broader paradigm shift toward cell plus matrix therapeutics, emphasizing controlled spatial localization and sustained paracrine dosing. $CD133^+$ progenitors represent a more refined autologous hematopoietic-derived population enriched for endothelial and angiogenic potential. These cells have been evaluated in trials including PERFECT, IMPACT-CABG, and Ixmyelocel-T [42-45]. Results reveal that $CD133^+$-enriched populations exert endothelial support, promote microvascular repair, and may reduce major adverse cardiovascular events, with the Ixmyelocel-T trial showing a 37% reduction in cardiac events at 12 months compared with placebo [44]. The 2024 Frontiers in Physiology meta-analysis highlights subgroup signals of modest but significant improvements in LV remodeling, particularly in ischemic cardiomyopathy [45].

Although direct cardiomyogenesis is absent, the consistent endothelial centric repair profile underscores the utility of $CD133^+$ progenitors in combined structural and microvascular restoration. Cardiac derived progenitor cells (CPCs) were initially proposed to serve as resident cardiomyogenic precursors, but definitive lineage tracing studies have disproven their ability to differentiate into new cardiomyocytes in vivo [46]. Instead, their value lies in their highly active reparative secretome, rich in growth factors, extracellular vesicles, and immunomodulatory signals. A central component of CPC-mediated benefit is the release of CPC derived exosomes, which demonstrate powerful cardioprotective, angiogenic, and anti-fibrotic effects [47,48].

Innovative biomaterial strategies have amplified CPC therapeutic potential. In rodent myocardial infarction (MI) models, injectable hydrogels delivered into the pericardial cavity form in situ cardiac patches that enhance the retention and reparative efficacy of iPSC-derived CPCs [41]. Cell sheet engineering is a scaffold-free myocardial repair strategy that enables generation of contractile, electrically coupled cardiac patches without exogenous biomaterials. Using temperature-responsive culture surfaces (typically poly(N-isopropylacrylamide, [PIPAAm]), confluent cardiomyocytes (or mixed cardiac cell populations) can be harvested as intact cell sheets while preserving extracellular matrix, cell-cell junctions, and surface receptors, thereby avoiding enzymatic dissociation and improving immediate functional integration after transplantation. Early landmark studies demonstrated that layering multiple cardiomyocyte sheets produces thick, synchronously beating tissue constructs with rapid formation of gap junctional coupling (connexin-43), establishing a biologically dense, pulsatile graft capable of improving myocardial function in preclinical injury models [49]. These scaffoldless cardiac patches represent a clinically relevant alternative to hydrogel or polymer-based constructs by leveraging the cell-produced matrix for mechanical cohesion and electromechanical continuity, while simplifying translational concerns related to biomaterial biocompatibility and degradation [50]. Collectively, CPCs exemplify the modern paracrine first paradigm, in which the cell functions primarily as a biological "minipump" for therapeutic factors rather than a contractile unit. Autologous induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) hold theoretical promise for true remuscularization due to their lineage fidelity and capacity for large scale generation. However, their translational deployment remains limited due to several major barriers:

1. Genomic instability and tumorigenic risk associated with reprogramming and expansion processes [51];

2. Arrhythmogenic potential, including triggered activity and conduction heterogeneity, particularly when immature grafts integrate with host myocardium, as emphasized in recent analyses of pluripotent stem cell-based cardiac repair [12].

3. Incomplete electrophysiologic and metabolic maturation, a problem extensively reviewed in tissue engineering and organoid models [52].

4. Hydrogel-enabled delivery and biophysical conditioning (electrical pacing, mechanical loading) can improve engraftment quality, yet full adult-like maturity remains elusive.

5. Notably, the addition of Leukemia Inhibitory Factor (LIF) during differentiation significantly improves PSC-CM viability by reducing Bax-mediated apoptosis and suppressing programmed cell death [17].

6. Ongoing progress in biomaterials, gene editing, and engineered maturation strategies may bring autologous iPSC-CMs closer to clinical feasibility, but substantial safety challenges remain.

Mechanisms Underlying Autologous Cell Benefits

Accumulated evidence from preclinical and clinical studies demonstrates that the therapeutic effects of autologous cell therapy arise predominantly from paracrine signaling rather than durable engraftment or transdifferentiation [32]. Autologous cell populations, including bone marrow mononuclear cells (BM-MNCs), mesenchymal stromal/stem cells (MSCs), cardiac-derived progenitor cells (CPCs), and induced pluripotent stem cell-derived progenitors (iPSC) secrete a diverse array of bioactive factors that modulate survival, angiogenesis, inflammation, and fibrosis. Key mediators include:

i. Pro-angiogenic growth factors: VEGF, HGF, and IGF-1

ii. Immunoregulatory cytokines: IL-10 and TGF-β

iii. Extracellular vesicles and exosomes enriched in cardioprotective and pro-repair microRNAs, such as miR-21, miR-210, miR-146a, and miR-132.

Exosomes have emerged as the principal effector of stem-cell-mediated cardiac repair. Balbi and Vassalli [48] clearly articulate that extracellular vesicles, rather than the transplanted cells

themselves, drive many of the observed functional improvements through modulation of endothelial function, attenuation of apoptosis, enhancement of angiogenesis, and immune rebalancing. This "exosome-centric" framework now dominates mechanistic understanding and is reshaping the design of next-generation biologics. Autologous MSCs and CPCs exert powerful immunomodulatory effects on the post-infarct microenvironment. MSCs are recognized for their ability to polarize macrophages toward an M2 reparative phenotype, shifting local cytokine production toward IL-10, ARG1, and YM1 [53-55] and suppress T-cell activation and proliferation, in part via secretion of PGE2, IDO, and TGF-β [56]. In addition, MSCs have the capacity to inhibit dendritic cell maturation and antigen presentation and modulate neutrophil infiltration and promote resolution of sterile inflammation. Collectively, these effects decrease infarct expansion and attenuate maladaptive post-MI remodeling. The importance of immunomodulation is underscored by consistent observations that MSC therapy improves functional outcomes even when engraftment is minimal or undetectable, highlighting the potency of inflammatory reprogramming as a therapeutic mechanism.

Autologous BM-MNCs and $CD133^+$ progenitor cells enhance microvascular perfusion and endothelial repair, representing a major pathway through which these cell types contribute to improved ventricular remodeling. $CD133^+$ cells, enriched for endothelial progenitors, secrete angiogenic factors and directly support neovascularization, increasing capillary density and limiting microvascular rarefaction in ischemic myocardium [57,58]. BM-MNCs have similarly been shown to augment microvascular repair by supplying endothelial primed subpopulations and by releasing paracrine mediators that activate endogenous endothelial cells4. Clinical correlations further support the primacy of this mechanism: reductions in LV remodeling in $CD133^+$ cell-treated patients occur in parallel with noninvasive markers of improved perfusion rather than increases in viable myocardium [59].

Autologous cells exert direct cytoprotective effects on cardiomyocytes and fibroblasts within the injured myocardium. A wide array of paracrine mediators (e.g., IGF-1, SDF-1, PI3K/AKT-activating signals) reduce early apoptotic loss in the peri-infarct zone [60-62]. Notably, Leukemia Inhibitory Factor (LIF) has emerged as a potent regulator of cardiomyocyte survival. [17] showed that LIF robustly reduces Bax-mediated apoptosis in pluripotent stem cell-derived cardiomyocytes by activating gp130-dependent survival pathways. In parallel, autologous MSCs inhibit pro-fibrotic TGF-β signaling in activated cardiac fibroblasts, reducing collagen I/III deposition, and preventing stiffening of the extracellular matrix [63,64]. The net effect is favorable remodeling characterized by smaller scar burden, preserved ventricular geometry, and improved systolic performance.

Clinical Evidence for Autologous Cell Therapy

A substantial body of clinical research has evaluated autologous cell therapies across ischemic and nonischemic cardiomyopathies. Evidence demonstrates signal-level functional improvement, heterogeneous efficacy, and consistent safety across platforms. Several well-conducted Phase I/II trials demonstrate modest but clinically relevant improvements in cardiac structure and function in select patient populations:

i. REGENERATE-DCM reported a 3-5% increase in LVEF following intracoronary infusion of autologous bone marrow-derived cells in nonischemic cardiomyopathy [15].

ii. The MPC-HF trial showed a dose-dependent reduction in heart failure-related hospitalization, with the 150-million cell group exhibiting significantly fewer HF major adverse cardiac events (MACE) [15].

iii. Ixmyelocel-T, an expanded autologous cell product enriched for $CD90^+$ MSCs and $CD14^+$ macrophages, yielded a 37% reduction in cardiac events at 12 months compared with placebo (RR 0.63; 95% CI 0.42-0.97).

These outcomes align with mechanistic observations that autologous therapies primarily influence remodeling, perfusion, and inflammation rather than direct myocardial regeneration. Not all autologous cell trials have demonstrated benefit. Key neutral studies include:

i. MiHeart, which found no significant differences in LVEF, LV volumes, or mortality between BM-MNC therapy and placebo in nonischemic cardiomyopathy [44].

ii. MSC-HF, in which autologous BM-derived MSCs did not significantly change LVEF despite modest reductions in LV end-systolic volume [39];

iii. PERFECT, evaluating $CD133^+$ progenitors during CABG, showed no improvement in LVEF or clinical endpoints at 180 days [42].

A consistent interpretative theme is inter-patient variability in cell potency, influenced by age, comorbidity, disease severity, and preexisting inflammatory burden. Such heterogeneity may limit the reproducibility of benefits across broader populations. Therapeutic responsiveness to autologous cell therapy is strongly time-dependent, as treatment delivered in the acute or subacute post-infarction phase targets a myocardium that is still biologically permissive (active inflammation, angiogenic signaling, and viable peri-infarct tissue), whereas therapy in chronic heart failure with mature scar occurs in a fibrotic, mechanically stiff, and poorly vascularized microenvironment that markedly limits cell retention and paracrine efficacy [42]. Across more than two decades of trials, autologous cell therapy has demonstrated an exceptionally strong safety record:

i. Arrhythmogenicity is low, especially compared with historical skeletal myoblast studies, which exhibited heightened ventricular tachyarrhythmia risk [65].

ii. No tumorigenicity has been reported despite concerns related to ex vivo cell expansion in some platforms.

iii. Procedure-related adverse events remain rare when cells are delivered intracoronary or via trans endocardial injection.

Importantly, autologous products avoid alloimmune reactions and do not require immunosuppression, supporting their continued evaluation as safe adjunctive therapies for heart failure management.

Emerging Technologies in Autologous Cardiac Regeneration

Exosomes derived from autologous MSCs, or cardiac progenitor cells (CPCs) have emerged as a compelling alternative to whole-cell transplantation. Their advantages include scalability, biological stability, and the absence of risks associated with uncontrolled differentiation or ectopic tissue formation. Unlike somatic cell products, exosomes can be standardized, stored, and delivered with much greater reproducibility, enabling consistent therapeutic dosing. Balbi and Vassalli (2020) provide a detailed framework demonstrating that exosomes constitute the primary functional unit of stem-cell-mediated cardioprotection, functioning through regulation of apoptosis, angiogenesis, inflammation, and metabolic remodeling. Early-phase clinical activity has begun to translate this paradigm into human investigation. For example, CAP-2003, an ongoing exosome-based trial, testing cardiosphere-derived extracellular vesicles for inflammatory and ischemic disorders [66]. These efforts position exosome-based therapeutics as a scalable, cell-free platform capable of delivering targeted biological signals without the logistical, regulatory, or safety challenges of live-cell products.

Biomaterial-enabled delivery systems have addressed one of the central limitations of autologous cell therapy: poor myocardial retention. Injectable hydrogels, especially those engineered for pericardial or intramyocardial localization, provide a biocompatible scaffold that enhances the persistence and bioactivity of transplanted cells or exosomes. [41] demonstrated that intrapericardial injection of decellularized extracellular matrix (ECM) or HA-based hydrogels forms a uniform in situ cardiac patch, significantly improving the retention and therapeutic effectiveness of iPSC-derived CPCs or MSC exosomes in rodent MI models. This biomaterial strategy decreases immune activation, boosts angiogenesis, and improves post-MI ventricular remodeling. As a minimally invasive intervention with translatability to fluoroscopy-guided human delivery, injectable hydrogels represent one of the most mature next-generation platforms for enhancing autologous cell efficacy.

The variability of autologous cell potency across patients has driven the adoption of advanced computational pipelines to characterize, predict, and optimize therapeutic response. As summarized by [2], cutting-edge methodologies now include:

i. Multi-omics profiling (genomic, epigenomic, transcriptomic, proteomic, and metabolomic signatures) to identify high-potency autologous cell subpopulations.

ii. Machine learning models to distinguish responder vs. non-responder patient phenotypes.

iii. Predictive analytics to optimize dosing, route of administration, and patient selection.

These advances, articulate a future in which autologous cell therapies are individually tailored, increasing both efficacy and reproducibility [3].

Genetic engineering technologies (e.g., CRISPR, lentiviral vectors, and epigenetic modulation) are increasingly applied to enhance the potency, homing, and survival of autologous cell products.

Promising strategies include:

i. Overexpression of pro-survival factors such as YAP or Cyclin D2, which enhance cardiomyocyte-like proliferation and stress resistance (PMID: 35614215) [BC1.1].

ii. Chemokine receptor engineering, particularly $CXCR4^{+}$ overexpression, which improves MSC homing to SDF-1-rich ischemic myocardium (PMID: 32747303) [BC2.1].

iii. Secretome engineering, enabling MSCs or CPCs to release enriched concentrations of anti-fibrotic or pro-angiogenic factors (e.g., VEGF, angiopoietin-1, miR-21).

Such modifications may allow autologous cells to achieve therapeutic effects at substantially lower doses while maintaining a favorable safety profile.

Future Directions

Personalization is emerging as a central theme in next generation cardiac repair. Integrating patient-specific omics, AI-based potency prediction, and customized exosome or cell formulations offer the potential for precision regenerative therapeutics tailored to individual biological signatures. Standardization remains a major barrier to clinical adoption. Establishing potency assays will be essential to ensure reproducible autologous therapies across diverse patient populations. Synergistic next generation approaches include:

i. Autologous MSCs engineered to deliver VEGF mRNA, enhancing neovascularization.

ii. CPC exosomes enriched with anti-fibrotic microRNAs, designed to suppress adverse remodeling.

These hybrid biologics may overcome the limitations of single modality therapies by simultaneously modulating multiple regenerative pathways. To advance the field, upcoming clinical trials must:

i. Incorporate MRI-based ventricular remodeling endpoints, which provide sensitive and reproducible measures of structural repair.

ii. Include ≥5-year follow-up to evaluate durability of benefit.

iii. Stratify enrollment using molecular, inflammatory, and genetic biomarkers to reduce responder heterogeneity.

Such rigorously designed trials will clarify which patient subsets benefit most from autologous biologics and help refine therapeutic indications.

Conclusion

Autologous cardiac cell therapy has evolved beyond the original vision of direct myocardial regeneration. Although early hopes for cell derived cardiomyogenesis were not realized, a robust body of evidence now supports the capacity of autologous biologics to improve cardiac structure and function through paracrine-mediated repair. Emerging technologies are redefining the scope of autologous cardiac regeneration. The field is shifting toward a signal centric paradigm, in which cells serve primarily as sources of targeted biological signals rather than structural building blocks. Through advances in manufacturing, mechanistic insight, and precision patient selection, autologous regenerative therapies may soon achieve the consistency, scalability, and efficacy required for widespread clinical adoption.

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Conflict of Interest

None.

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