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Commentary

Fibroblast to endothelial transdifferentiation: A microvascular mechanism of cardiac recovery

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Abstract

Heart failure affects more than 64 million people worldwide and remains a leading cause of cardiovascular mortality. In a landmark study published in Circulation, Li and colleagues demonstrate that recovery from heart failure, modeled by left ventricular assist device support in humans and pharmacological reversal in mice, is fundamentally a microvascular phenomenon driven in part by mesenchymal to endothelial transition (MEndoT) of cardiac fibroblasts. Integrating single nucleus RNA sequencing, genetic lineage tracing, patient derived nonmyocyte cultures, and functional microsphere perfusion, the authors identify c-Myc as a key molecular mediator of this fibroblast to endothelial fate switch. This commentary appraises the novelty, methodology, principal findings, and limitations of this work, and considers what it may and may not yet tell us about the biology of microvascular aging in the failing heart.

Keywords: Heart failure, microvascular remodeling, mesenchymal-to-endothelial transition, cardiac fibroblasts, endothelial regeneration, c-Myc, inflammaging, cardiac recovery

INTRODUCTION

Heart failure represents one of the most formidable challenges in contemporary cardiovascular medicine, affecting more than 64 million people globally and carrying a prognosis that rivals many advanced malignancies[1]. Despite decades of progress in neurohormonal blockade and device therapy, the fundamental biology of cardiac performance recovery remains incompletely understood. The prevailing framework attributes functional improvement primarily to cardiomyocyte-level changes, including reduced wall stress, normalization of calcium handling, and reversal of maladaptive hypertrophy, and has historically underemphasized the potential contribution of nonmyocyte populations to structural and vascular repair[2,3].

This cardiomyocyte centric view is increasingly difficult to reconcile with the structural evidence emerging from left ventricular assist device studies in humans. Human explant analyses and paired transcriptomic studies have demonstrated that device support is associated not only with improved pump function but with reduced interstitial fibrosis, increased capillary density, and transcriptomic signatures consistent with nonmyocyte cell fate transitions , changes that extend well beyond what cardiomyocyte salvage alone can explain[2,3]. The cardiac interstitial space, comprising fibroblasts, endothelial cells, and the extracellular matrix, and their dynamic interactions, appears to be an active participant in structural recovery. These observations suggest that cardiac recovery may reflect coordinated remodeling across multiple non-myocyte populations rather than solely restoration of cardiomyocyte function.

Extending the biological significance of this question is its close association with aging. The failing heart and the aging heart share a striking convergence of pathological features: progressive capillary rarefaction, interstitial fibrosis, and impaired angiogenic responsiveness[4,5]. Age is the single most powerful nonmodifiable risk factor for heart failure

and understanding whether the microvascular repair mechanisms activated during recovery are preserved or attenuated in older individuals is a question of direct clinical importance.

In a rigorously executed study now published in Circulation, Li and colleagues address the cellular identity of this repair program directly, providing the first single cell resolution evidence, spanning human explant tissue, *in vivo* murine genetic lineage tracing, and *in vitro* patient derived nonmyocyte cultures, that cardiac fibroblasts actively transdifferentiate into endothelial cells during device supported recovery[6]. This commentary examines that evidence critically and considers its implications for the cardiovascular aging field.

SIGNIFICANCE OF THE RESEARCH QUESTION

The failing heart undergoes progressive structural remodeling that is not simply a consequence of impaired contractile function but also contributes to the perpetuation and progression of heart failure. Capillary rarefaction reduces oxygen delivery to viable myocardium, interstitial fibrosis increases myocardial stiffness and impairs diastolic relaxation, and the exhaustion of the angiogenic reserve limits the capacity for endogenous vascular repair[4,5]. These structural changes mirror, in accelerated form, the microvascular and fibrotic remodeling that occurs in the aging myocardium, implying shared underlying mechanisms that remain incompletely characterized.

The left ventricular assist device has emerged as an unexpected tool for interrogating these mechanisms. As a mechanical bridge to transplantation, device support unloads the failing ventricle and, in DOIng so, initiates a program of structural recovery that includes fibrosis regression, capillary expansion, and diminished myocardial hypertrophy, findings documented in paired human explant studies and large observational cohorts[2,3]. What has remained elusive is the identity of the cells driving this structural remodeling and the molecular signals that orchestrate it. Li and colleagues address this gap with a multimodal experimental strategy that establishes a cellular and molecular framework for cardiac microvascular recovery, a process whose interaction with aging has yet to be systematically investigated[6]. Clinically, device support yields a spectrum of outcomes, from sustained myocardial recovery that permits device explantation to persistent device dependence, and

whether an endogenous regenerative program of this kind distinguishes these divergent trajectories remains unanswered.

CONCEPTUAL INNOVATION AND EXPERIMENTAL STRATEGY

The study's principal conceptual contribution is demonstrating, for the first time, at single cell resolution in recovering human myocardium, that a defined cardiac fibroblast subpopulation actively transdifferentiates into endothelial cells during device supported recovery[6]. Substantial evidence from human tissue analyses and *in vivo* murine studies supports a central role for endothelial-to-mesenchymal transition (EndMT) in the development of cardiac fibrosis[7,8].

While MEndoT has been proposed to contribute to cardiac neovascularization after myocardial infarction[9], subsequent lineage-tracing studies employing rigorous pulse-chase methodologies have challenged the magnitude of this effect[10]. Against this backdrop, the demonstration of MEndoT in the recovering human heart at single-cell resolution, supported by *in vivo* causal validation, represents a noteworthy advance. The central framework of the study — spanning experimental platforms, key findings, mechanistic implications, and future directions — is summarized in Figure 1.

Human tissue. The human component included 24 patients with end-stage heart failure undergoing device implantation as a bridge to transplantation; and standardized mid-myocardial biopsies were collected, and fibrosis was quantified in a blinded manner[6].

Single-nucleus RNA sequencing. Single-nucleus RNA sequencing was performed on pooled nuclei from five pre-device and five post-device patients for transcriptomic discovery[6]. Data integration and batch correction were benchmarked against established human cardiac cell atlas references[11,12]. Independent validation was performed in a non-pooled paired cohort of five patients with documented functional recovery by improved ejection fraction[6], a critical replication step that substantially mitigates the principal vulnerability of pooled single nucleus designs.

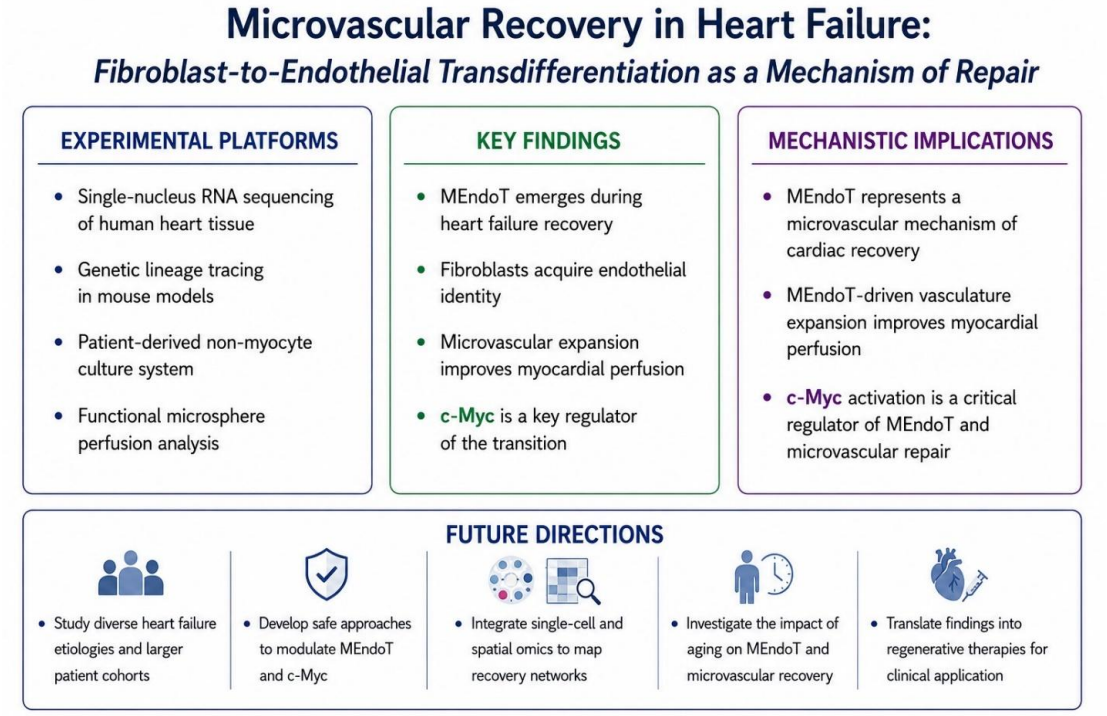

Figure 1. Summary of the experimental platforms, key findings, mechanistic implications, and future directions. Created with AI-driven BioRender (www.biorender.com).

Murine model. A pharmacological heart failure model, oral L-NAME and dietary salt loading combined with subcutaneous angiotensin II infusion, an approach previously validated for studying mesenchymal endothelial transitions in the heart[13], produced a robust nonischemic cardiomyopathy phenotype. Ejection fraction fell from 56% to 36% (p = 0.001) and normalized by week 9 following drug withdrawal[6]. Microvascular volume was quantified using fluorescent microsphere bead perfusion[14], a technique that provides physiologically meaningful, perfusion based evidence of vascular restoration that complements and extends conventional capillary density histology.

Genetic lineage tracing. The causal centerpiece of the study was a genetic lineage tracing experiment using Col1a2-creERT:R26R-tdTomato mice, in which tamoxifen induction permanently and irreversibly marks Col1a2 expressing cardiac fibroblasts with a tdTomato fluorescent reporter[6]. The subsequent detection of CD31 positive, tdTomato positive dual positive cells, indicating fibroblast origin endothelial identity, by immunohistochemistry,

flow cytometry, and confocal three dimensional colocalization in recovering but not control hearts constitutes the most definitive *in vivo* causal evidence of MEndoT in this study[6].

PRINCIPAL FINDINGS

Human explant tissue. Post device myocardium showed significantly reduced fibrosis (10% *vs.* 19%, $p = 0.03$), fewer fibroblasts per low power field (66 *vs.* 99, $p < 0.0001$), and greater endothelial cell density (97 *vs.* 75, $p < 0.01$) relative to pre device tissue, quantified by blinded computerized histomorphometry[6]. A significant negative Pearson correlation between fibroblast and endothelial cell abundance across the cohort ($r = -0.76$, $p = 0.01$) provided the first tissue level quantitative signal of a reciprocal cellular relationship[6]. Pseudotime trajectory analysis of the single nucleus RNA sequencing data identified a directional shift from the EC5 endothelial subtype toward the FB2 fibroblast subtype pre device, consistent with endothelial to mesenchymal transition as a promoter of fibrosis in the failing state, with the reverse FB2 to EC5 transition emerging post device, accompanied by transcriptomic downregulation of fibrosis associated genes and upregulation of angiogenic programs[6]. Healthy donor hearts showed minimal evidence of either transition, confirming their disease state specificity[6,15].

Murine model. Microvascular volume assessed by fluorescent microsphere perfusion[14] was significantly reduced in heart failure (6.9% *vs.* 10.8% in healthy controls, $p < 0.0001$) and fully restored during pharmacological recovery (10.5%, $p < 0.0001$ *vs.* heart failure), with interstitial fibrosis following the reciprocal temporal pattern[6]. These *in vivo* perfusion data confirm that the changes in cellular composition identified by single nucleus RNA sequencing correspond to functionally meaningful differences in microvascular perfusion capacity.

Genetic lineage tracing. Col1a2 lineage marked fibroblast derived endothelial cells were detected in recovering hearts at 5.63% of all CD31 positive cells, compared with only 0.45% in nonfailing controls ($p < 0.0001$), providing direct *in vivo* causal evidence of MEnoT during cardiac recovery[6]. This proportion is likely an underestimate given the inherent incomplete efficiency of tamoxifen inducible Cre recombination systems.

Patient-derived nonmyocyte cultures. Functional causality of c-Myc in the MEnoT program was established through bidirectional perturbation experiments in human patient derived cardiac nonmyocytes[6]. siRNA mediated knockdown of c-Myc in post device nonmyocytes impaired cellular proliferation and disrupted vessel-like network organization. Conversely, c-Myc overexpression in pre device nonmyocytes enhanced proliferation, promoted tubulogenesis, and generated COL1A2 positive, CD144 positive double positive fibroblast derived endothelial cells *in vitro*[6]. Complementing these functional data, cell-cell communication analyses of the single nucleus RNA sequencing dataset identified increased FB2 to EC5 signaling through LAMA2 integrin (ITGA/ITGB) ligand receptor pairs post device, implicating the extracellular matrix as an active permissive participant in enabling MEndoT *in vivo*[6,16].

MECHANISTIC SIGNIFICANCE AND AGING RELEVANCE

The identification of c-Myc as a functional mediator of MEndoT is well grounded in prior experimental literature[17,18]. *in vivo* developmental studies have established that germline c-Myc deletion causes severe vascular defects and embryonic lethality, demonstrating its essential role in vasculogenesis and angiogenesis[17]. Endothelial-specific c-Myc overexpression in mouse embryos produced lethal vascular edema and hemorrhage, demonstrating that precise c-Myc dosage is required for normal vascular permeability and remodeling during development[19], and combined *in vivo* and *in vitro* cardiac studies showed that c-Myc is specifically required for coronary vascular morphogenesis through cell type specific transcriptional programs[18]. Its identity as one of the four original Yamanaka reprogramming factors, established in landmark *in vitro* fibroblast reprogramming experiments across mouse and human cells[20], further positions it as a plausible orchestrator of fibroblast cell state switching. Within the transitioning FB2 to EC5 population identified by single nucleus RNA sequencing[6], antifibrotic transcriptomic changes, including downregulation of transforming growth factor-beta 1 (TGF-β1)[21], connective tissue growth factor (CCN2/CTGF)[22], angiotensin II receptor type 1 (AGTR1)[23], and Periostin[24], converge with the acquisition of endothelial identity, suggesting that fibrosis regression and

capillary expansion are mechanistically coupled during recovery rather than independent parallel processes.

For the cardiovascular aging field, the most consequential question raised by these findings is one the study does not directly address: does MEndoT capacity decline with age, and could its attrition contribute to the diminished microvascular repair capacity of the aging failing heart? Two lines of prior evidence make this concern tangible. First, *in vivo* murine studies have demonstrated that aged cardiac fibroblasts accumulate senescence markers and lose transcriptional plasticity[25], and *in vivo* mouse myocardial infarction models have shown that senescent cardiac fibroblasts promote maladaptive fibrotic remodeling[26], changes that could, in principle, suppress the FB2 to EC5 transition identified here. Second, histological and biochemical analyses of human and rodent cardiac tissue have shown that the laminin isoform composition and integrin expression profile of the cardiac interstitial phenotype shift with aging toward configurations associated with fibrosis rather than angiogenesis[27], suggesting that the LAMA2 integrin signaling axis that appears to permissively enable MEndoT *in vivo*[6] may itself be disrupted in aged myocardium. If so, cell intrinsic interventions targeting c-Myc alone may prove insufficient in older patients, and restoration of the permissive extracellular matrix niche may be an additional requirement. These are hypotheses that the present study motivates but does not test. More broadly, they point toward coordinated interactions among multiple cardiac non-myocyte populations—extending beyond the fibroblast-endothelial axis—as a determinant of the reparative microenvironment, a possibility that warrants future investigation.

LIMITATIONS AND FUTURE DIRECTIONS

Limitations

Several methodological considerations constrain the conclusions that can be drawn from this study. The unpaired single nucleus RNA sequencing discovery design, comparing pre device samples from one patient group with post device samples from a different group, leaves open the possibility that interindividual transcriptomic differences, rather than the device intervention itself, partly account for the observed cell state transitions. The independent paired validation cohort partially addresses this concern, but the small sample sizes in both

cohorts limit the generalizability of the findings across the full spectrum of device supported patients, including those with ischemic versus nonischemic etiology, varying degrees of functional recovery, and differing comorbidity burdens[6].

The murine model recapitulates the hemodynamic and structural features of nonischemic cardiomyopathy but not ischemic heart disease, a distinction with potential mechanistic significance. Using a pulse-chase genetic lineage tracing strategy with more stringent temporal labeling, He and colleagues found that post-injury coronary neovascularization in a myocardial infarction model was attributable primarily to proliferation of preexisting endothelial cells, with no significant contribution from mesenchymal lineages[10], a result that may reflect methodological differences in Cre driver specificity compared with the constitutive lineage tracing approach used in prior MEndoT studies[9]. This discordance raises the important question of whether the MEnoT program described by Li *et al.* is specific to nonischemic, hemodynamically driven forms of heart failure. Furthermore, pharmacological recovery in mice and device mediated hemodynamic unloading in humans engage distinct mechanosensitive signaling pathways. Focal adhesion kinase mediated stretch signaling has been characterized *in vitro* and *in vivo* cardiomyocyte studies[28], while *in vitro* studies of cardiac fibroblasts on tunable matrix substrates have shown that substrate stiffness independently governs profibrotic fibroblast phenotype[29]. Mechanistic parallels between these two recovery paradigms should therefore not be assumed without direct experimental comparison.

Finally, the oncogenic potential of c-Myc is well established, and its therapeutic activation warrants particular caution in older patients with heart failure, among whom clonal hematopoiesis, itself associated with accelerated heart failure progression in both *in vivo* mouse models and human clinical data, is highly prevalent[30].

The absence of age as a systematically analyzed biological variable is a meaningful gap for this journal's readership. Whether the MEndoT competent FB2 fibroblast subpopulation is depleted, epigenetically silenced, or phenotypically altered in aged myocardium, and whether aging modifies the efficiency of c-Myc driven trans-differentiation *in vitro* or *in vivo*, remain

open questions of direct clinical relevance that dedicated follow-up studies will need to address.

Future directions

Future research should focus on validating fibroblast-to-endothelial MEndoT across diverse heart failure etiologies, including ischemic, hypertensive, diabetic, aging, and genetic cardiomyopathies, using larger and more representative patient cohorts. Although MEndoT represents an important mechanism of vascular repair, myocardial recovery is likely to result from the coordinated contribution of multiple regenerative pathways. Advanced single-cell, spatial transcriptomic, and multi-omics technologies will be essential for mapping the cellular networks and molecular pathway.

Importantly, microvascular regeneration during recovery may not reduce to a single fibroblast-to-endothelial conversion but instead reflect coordinated interactions across the entire cardiac non-myocyte compartment, a possibility that future studies should directly test. Attention should be paid to defining the precise role of c-Myc and identifying safer, more targeted approaches to modulate its activity, given concerns regarding long-term safety and oncogenic potential. In addition, studies are needed to optimize therapeutic delivery strategies, evaluate the durability of newly formed vasculature, and determine whether enhancing MEndoT can improve long-term cardiac function. A parallel priority will be translational: determining whether transcriptomic or circulating biomarkers of MEnoT can measure this program in patients, identify those most likely to achieve meaningful recovery, and anchor regenerative therapy selection to hard clinical endpoints such as device explantation, transplant-free survival, and heart failure hospitalization. Ultimately, translating these mechanistic insights into clinically applicable regenerative therapies may open new avenues for promoting myocardial repair and recovery in patients with heart failure.

CONCLUSIONS

Li and colleagues have produced a carefully executed and conceptually important study that reframes cardiac recovery as a fundamentally microvascular and cell plasticity phenomenon[6]. By integrating human explant transcriptomics, *in vivo* murine genetic lineage

tracing, and *in vitro* patient derived nonmyocyte functional assays, they provide compelling evidence that a defined fibroblast subpopulation undergoes MEnoT during device supported recovery, contributing simultaneously to capillary expansion and fibrosis regression. This mechanistic coupling challenges the myocyte-centric paradigm of heart failure pathobiology and introduces a new therapeutic axis centered on non-myocyte cell fate regulation. The clinical value of these findings will ultimately depend on whether this regenerative program can be harnessed to identify, predict, or enhance meaningful myocardial recovery in patients with heart failure. The identification of c-Myc as a functional mediator across both *in vivo* and *in vitro* experimental systems provides a tractable molecular target[6]. Advances in transient mRNA delivery via lipid nanoparticles offer a plausible route toward fibroblast restricted, temporally controlled c-Myc activation, though the oncogenic liabilities of this approach will require careful preclinical evaluation, particularly in aged animals with established clonal hematopoiesis.

For the cardiovascular aging field, the most important contribution of this work may ultimately be conceptual: the establishment of an endogenous microvascular repair pathway in the failing heart[6]. Whether that pathway is intact, attenuated, or functionally exhausted in aged myocardium, and whether it can be restored by targeting the molecular or matrix level mechanisms identified here, are questions this study places firmly on the research agenda. Answering them will require dedicated investigation in aged preclinical *in vivo* models and age stratified clinical cohorts, and such work is a prerequisite for responsible therapeutic translation of these findings.

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Authors' contributions

Conceptualization; investigation; formal analysis; writing – original draft; supervision; editing: Wang MY;

Writing – review & editing: Monticone RE;

Writing – review & editing; clinical and translational perspective: Baca GL.

Availability of data and materials

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

AI and AI-assisted tools statement

During the preparation of this work, the authors used AI tools (ChatGPT and Claude) for the purpose of language editing and improving readability. After using these tools, the authors reviewed and edited the content as necessary and took full responsibility for the content of the publication.

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Conflict of interest

The authors declare no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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