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Myocardial Recovery versus Myocardial Regeneration: Mechanisms and Therapeutic Modulation

REVIEW

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ABSTRACT

Myocardial recovery is characterized by a return toward normal structure and function of the heart after an injury. Mechanisms of myocardial recovery include restoration and/or adaptation of myocyte structure and function, mitochondrial activity and number, metabolic homeostasis, electrophysiological stability, extracellular matrix remodeling, and myocardial perfusion. Myocardial regeneration is an element of myocardial recovery that involves the generation of new myocardial tissue, a process which is limited in adult humans but may be therapeutically augmented. Understanding the mechanisms of myocardial recovery and myocardial regeneration will lead to novel therapies for heart failure.

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THE DIFFERENCE BETWEEN MYOCARDIAL RECOVERY AND MYOCARDIAL REGENERATION

Myocardial recovery is characterized by a return toward normal structure and function of the heart after an injury.[1] A dramatic example of such recovery is seen when an acute occlusion of an epicardial coronary artery is successfully reversed by timely endovascular therapy.[2] Initially, the stunned myocardium is dysfunctional from the pathophysiology induced by ischemia-reperfusion. However, within hours to days, partial or even full recovery of myocardial function may be observed. Partial recovery of myocardial function is commonly observed in patients whose heart failure is optimally treated medically with angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists (with or without a neprilysin inhibitor), beta-adrenergic antagonists, and aldosterone antagonists.[3] Mechanisms of myocardial recovery include restoration and/or adaptation of myocyte structure and function,[4-7] mitochondrial activity and number,[8-10] metabolic homeostasis,[11] electrophysiological stability,[12] extracellular matrix remodeling,[13] and myocardial perfusion.

Most recently, the sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to reduce the risk of major adverse cardiovascular events in patients with heart failure.[14] These agents may have an effect on cardiovascular recovery by reversing aberrations in the uptake and/or metabolism of glucose, long-chain fatty acid, and amino acids. In addition, they may restore mitochondrial homeostasis, thereby reducing the accumulation of deleterious metabolites. Finally, these drugs may promote nutrient-deprivation signaling and improve iron disposition, which are impaired in heart failure.

Myocardial regeneration can play a role in myocardial recovery. Myocardial regeneration involves the generation of new myocardial tissue, a process that is limited in adult humans but might be therapeutically augmented. Myocardial regeneration may include myocyte proliferation, angiogenesis, and extracellular matrix generation and may be enhanced by resident or circulating stem cells.[6] In addition, infiltrating M2 macrophages facilitate the resolution of inflammation, modulate the generation of extracellular matrix, and enhance the proliferation of myocytes and vascular cells.[15] Experimental efforts to therapeutically enhance myocardial regeneration include the intravascular or intramyocardial administration of human stem cells,[16] the use of small molecules or genetic therapies to stimulate myocyte proliferation, and the use of bioengineered tissue.[17,18] What follows are some insights into myocardial regeneration that we and others have gained in studies of animal and human models of myocardial regeneration.

MYOCARDIAL RECOVERY: INSIGHTS ON LEFT VENTRICULAR ASSIST DEVICES

LEFT VENTRICULAR ASSIST DEVICES AND MYOCARDIAL RECOVERY

Heart failure (HF) currently affects approximately 6.5 million adults in the United States (US), with direct costs of $21 billion.[19] Strategies to regenerate or recover the failing heart are heavily investigated. Recent success in pharmacological development with sodium-glucose cotransporter (SGLT) inhibitors indicates that significant opportunities exist for therapeutic advances in medical therapy.[20] However, for end-stage HF patients, heart transplantation remains the best option to improve cardiac function and quality of life.[21,22] Due to the limited number of donor hearts and existing risk factors and comorbidities, this option is not immediately available for most patients.[23]

Accordingly, implantation of mechanical circulatory support (MCS) devices, including left ventricular assist devices (LVADs), can be used for cardiac support as a bridge to transplantation, although their use has declined in recent years.[24] Indeed, MCS has also been approved as a destination therapy without intended bridging to transplantation by the US Food and Drug Administration since 2010[25] for advanced HF patients, which has increased the overall use of MCS. Intriguingly, with LVAD support, the native heart undergoes structural and functional improvement with so-called "reverse remodeling."[26-28] While the mechanisms by which mechanical unloading leads to myocardial recovery are still under investigation, the possibility of myocardial recovery from heart failure is evident. Understanding the endogenous mechanisms of this recovery may facilitate pharmaceutical, biological, or cellular therapies to augment these recovery mechanisms and transform HF therapies.

HISTOLOGICAL AND MOLECULAR HALLMARKS OF RECOVERY

At the time of LVAD implantation, the apical core that is removed can be harvested for study (pre-LVAD tissue). Later, when the patient undergoes LVAD explant and allograft transplantation, the native heart can be harvested (post-LVAD tissue) and compared to the pre-LVAD tissue in the same patient (paired samples). Although complete cardiac recovery by LVAD implantation is rare,[29] varied degrees of functional and structural improvement are observed in the post-LVAD heart.[28,30] We and others have observed a reduction in myocyte size (ie, a regression of the abnormal myocyte hypertrophy), as well as a reduction in interstitial fibrosis and an increase in capillary density (Figure 1), particularly in those patients with nonischemic heart failure.

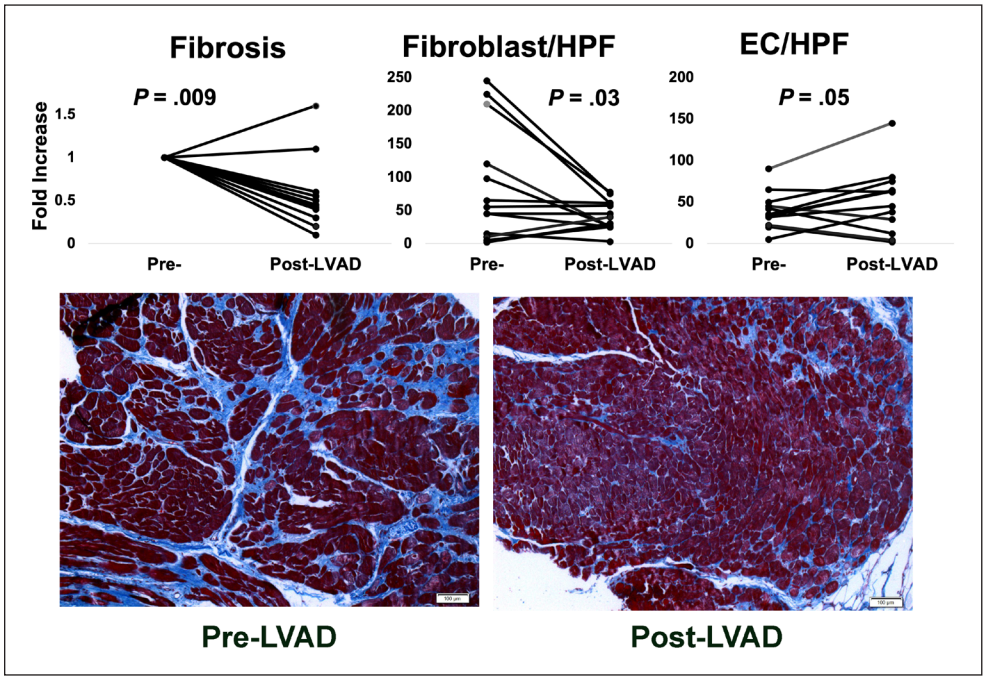

Figure 1 Left ventricular tissue from heart failure patients supported by LVAD demonstrates a decrease in fibrosis compared to that seen in their pre-LVAD sample (paired patient samples used). This decrease is accompanied by a reduction in fibroblast cell count per HPF and a concomitant increase in EC number. The decrease in fibrosis (blue) is visually evident using Masson's Trichrome staining. LVAD: left ventricular assist device; HPF: high-power field; EC: endothelial cells (original figure)

Drakos and colleagues used global RNA-seq and phosphopeptide profiling in LVAD responders, nonresponders, and healthy donors to identify unique transcriptional and phosphoproteomic markers associated with recovery.[31] They observed 29 transcripts and 93 phosphopeptides in patients with HF, which distinguished those patients that were likely to have the most improvement in cardiac function and structure after LVAD implantation. These markers were consistent with differential regulation of cell cycle and extracellular matrix/focal adhesions. Whether these pathways are potential mediators of recovery, or merely markers, remains to be resolved.

In a subsequent study that performed scRNA-seq studies of similar patient samples, Amrute et al. identified cell-type specific signatures during recovery, most prominently in macrophages and fibroblasts.[32] Within these cell types, inflammatory signatures were negative predictors of recovery, whereas downregulation of RUNX1, a regulator of cell differentiation, was associated with recovery. In silico and murine studies confirmed a role for RUNX1 downregulation in macrophages and fibroblasts as a potential determinant of recovery. Thus, RUNX1 might be a novel therapeutic target to enhance heart recovery. Although the studies by Drakos and Amrute are of interest, their findings need confirmation in light of the small numbers of patients involved and the heterogeneity of the samples, together with confounding variables such as those introduced by the complexity of tissue collection.

MYOCARDIAL RECOVERY AND REGENERATION: INSIGHTS FROM PRE-CLINICAL MODELS

MOUSE MODEL OF MYOCARDIAL RECOVERY

We have mimicked the phenomenon of post-LVAD recovery in a murine model of HF.[33] In this model, the HF is induced by infusions of angiotensin II and L-NAME (an inhibitor of nitric oxide synthase; NOS) together with high salt intake. The mice develop HF after 5 weeks based on clinical and echocardiographic criteria. Histology reveals interstitial and perivascular fibrosis. After the withdrawal of the infusions and high-salt diet, the animal recovers as evidenced by echocardiography and histological analysis. Findings from transcriptional profiling (bulk RNA-seq) are consistent with an endothelial-to-mesenchymal transition during the induction of HF, which is reversed during the recovery phase.

This model of HF and HF recovery is quite different from the murine myocardial infarction (MI) model in which recovery is limited.[34] Our model is more consistent with the recovery that can be observed in patients with nonischemic HF.[35] That said, this murine model is imperfect in that the duration of human nonischemic cardiomyopathy is much longer and because LVAD recipients are treated with components of guideline-directed medical therapy (GDMT). Nevertheless, our murine model replicates processes that appear to be involved in recovery from human HF, including normalization of myocyte structure and function, and

reduced interstitial fibrosis. Additionally, in unpublished data, we have observed recovery of the microvasculature in the murine model and in the post-LVAD human heart, which may enhance myocardial perfusion and HF recovery.

MODELS OF MYOCARDIAL REGENERATION: LESSONS FROM DEVELOPMENT

Regeneration of myocardial tissue after injury has not been observed in the adult human heart. In contrast, such regeneration after injury is observed in lower vertebrates. Furthermore, myocardial regeneration can be observed in mammals at an early stage of development (ie, postnatal mice and pigs). Although myocardial regeneration does not occur in adult mammals, it is useful to study this process in post-natal mammals and lower vertebrates as the pathways mediating such regeneration might be therapeutically exploited in humans for recovery from myocardial injury and HF.

In lower vertebrates, including teleost fish and urodeles, regeneration of the heart is possible throughout adulthood.[6] However, mammals lose their ability to regenerate the heart soon after birth.[36] In mice, this regenerative window is within 1 week post-postpartum. At later time points, regenerative capacity is rapidly lost, and a fibrotic rather than a regenerative response is dominant.[37] In swine, this regenerative window is further narrowed to 2 days post-partum.[38,39] However, a pig study from Zhao et al. suggested that the regenerative window can be extended if there is an early injury to the heart (in this case, an apical resection). The investigators observed that this early injury facilitated a more complete recovery from an MI-induced 1 month later.[40] This observation suggests that mechanisms can be activated to extend the regenerative window in mammals. In humans, a few case reports demonstrated complete cardiac recovery after massive MI occurring in the neonatal period.[41-43] This suggests that the shift from hyperplastic to hypertrophic growth of cardiomyocytes during the adaptation to the oxygen-rich environment post-partum fundamentally changes their ability for damage repair.[44, 45]

A metabolic mechanism may underlie the regenerative difference between the fetal/neonatal and adult heart. The cardiomyocyte (CM) metabolism switched from glycolysis to fatty acid oxidation quickly after birth. The mitochondria production of reactive oxygen species from elevated oxidative phosphorylation is believed to contribute to the CM cycle arrest that limits cardiomyogenesis in adults. A study conducted by Cardoso et al. demonstrated that inhibiting fatty acid oxidation could extend the regenerative period in neonatal mice. Additionally, another study suggested that the knockout of cardiac-specific pyruvate dehydrogenase kinase 4, an enzyme that suppresses glucose utilization via mitochondrial pyruvate dehydrogenase, promotes cardiomyocyte proliferation following MI in adult mice.[46]

A recent study by Li et al. reported a similar role of fatty acid oxidation inhibition of cardiac regeneration but focused on another essential enzyme, carnitine palmitoyltransferase (Cpt1b).[47] Cpt1b is the rate-limiting enzyme for fatty acid oxidation. When this enzyme was knocked out in CM, the adult mice exhibited very little scar formation in the ischemia-reperfusion model and showed significantly greater functional recovery. The authors further demonstrated the metabolic alteration in the KO mice results in an accumulation of α-ketoglutarate (α-KG) and α-KG-dependent activation of H3K4 demethylase KDM5, prompting heart regeneration by reducing CM maturity and enhancing CM proliferation.

Other strategies repressing oxidative phosphorylation targeting Pkm2,[48] Pitx2,[49] and SDH[50] are also reported to facilitate cardiac regeneration post-injury. A better understanding of the mechanisms facilitating regeneration in young mammals may permit us to therapeutically modulate these mechanisms to enhance true cardiovascular regeneration in adults.

INJURY MODELS TO STUDY CARDIOVASCULAR REGENERATION

Different models have been generated to elucidate intrinsic regenerative mechanisms that might facilitate heart failure treatment (Figure 2). To induce neonatal cardiac regeneration, injury methods including apical resection, left anterior descending artery ligation (LAD), and cryoprobe-induced infarction are being explored.[51,6,52] Compared with cryoinjury,[53] apical resection[37] and coronary artery ligation-induced myocardial infarction[54] are reported to render better regenerative responses in mouse pups.[55] The use of proteomics, epigenomics, and spatiotemporal transcriptional profiling have identified novel regulators that promote cardiac regeneration. For example, Wang et al. used transcriptomic analysis and histone mark H3K27ac ChIP-seq to compare the regenerative responses in mice that undergo LAD within (P1) or out of the regenerative window (P8). This study identified an RNA-binding protein, IGF2BP, secreted by macrophages, to be critical in promoting cardiovascular proliferation.[56] The same group later conducted snRNA and snATAC-seq to perform similar comparisons and identified a macrophage-secreted factor CLCF1 in facilitating cardiovascular proliferation.[57]

ENGINEERED HEART TISSUE TO MODEL REGENERATION

To mimic human cardiac diseases in vitro or ex vivo, 3-dimensional (3D) culture-based cardiac tissue models that integrate bioengineering and stem cell technology

have facilitated progress in this field.[58-60] The engineered heart tissue (EHT) can be generated as a 3D cell culture of human CMs together with non-myocytes grown in extracellular matrix hydrogel.[59] Typically, the myocytes and non-myocytes are differentiated from human-induced pluripotent stem cells (iPSCs). Yamanaka and colleagues have previously shown that forced expression of four transcriptional factors (Oct4, Sox2, KLF4, and cMyc;OSKM) could generate iPSCs from somatic cells.[61-64] These iPSCs can be differentiated into any cell type, including cardiovascular cells. When the myocytes and non-myocytes are placed in the hydrogel matrix, they self-assemble into a myocardial tissue with immature electrophysiological and contractile properties.

With electrical excitation,[65] relatively more mature CMs can be induced in the EHT to be used for histological and functional analysis.[66] EHT has thus been used for drug screening[67] and further in patient-specific pathophysiology.[68,69] As EHT incorporates multiple cell types including cardiomyocytes, fibroblasts, and endothelial cells,[70] studying the signal exchanges among different cell types in the cardiac microenvironment could be useful.[71] Although the current methodologies only use patient-derived iPSC, which will be further differentiated into CMs,[72] it is possible that more cell types that directly derive from patients could be incorporated into this model to better mimic the in-situ environment during disease. (See Figure 2).

MOLECULAR DETERMINANTS OF CARDIOVASCULAR REGENERATION

A strategy arising from the study of regeneration in young mammals is to reactivate fetal transcriptional programs to combat heart injury in adults. Chen et al.[73] generated a transgenic animal in which cardiomyocytes could express the pluripotency factors OSKM in a doxycycline (Dox) inducible manner. The hypothesis is that transient induction of the pluripotency factors in the CMs might "turn back the clock" to a less mature CM that may be more capable of cell division in response to an injury. Indeed, the authors found that a short-term (6 days) administration of Dox induced OSKM in the CMs of the transgenic animal. The expression of these pluripotency factors in the CMs caused their partial dedifferentiation and cell-cycle reentry without causing neoplasms or hyperplasia. When applying this reprogramming strategy during different stages after LAD ligation, they observed increased CM proliferation, reductions in cardiac fibrosis, and improved cardiac function. Thus, the adult murine myocardium is capable of greater regeneration and repair with transient expression of the pluripotency factors in the CMs.

In addition to playing an essential role in extracellular matrix deposition and fibrosis,[74] fibroblasts may be reprogrammed into various cell types during cardiovascular regeneration.[75,76] A study from Ye et al. reported a method to reprogram human cardiac fibroblasts (CF) into iPSC in vitro. The fibroblast-derived iPSCs were then differentiated in vitro into cardiomyocytes (iCM)

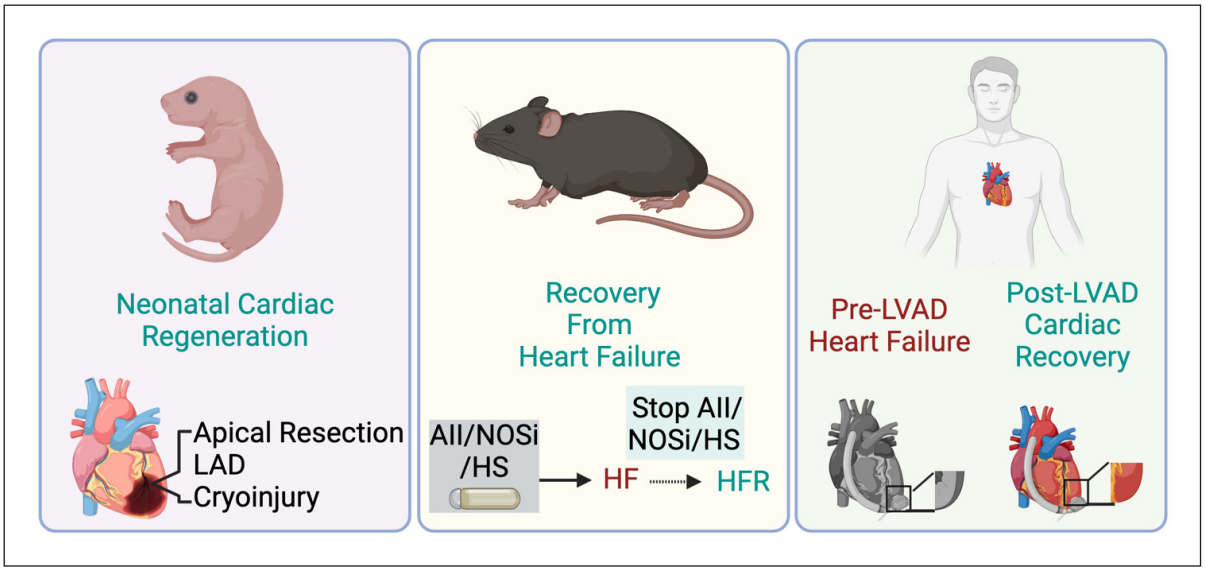

Figure 2 Models of cardiovascular regeneration and recovery. Neonatal mice have the intrinsic ability to regenerate the heart within 1 week of birth. Apical resection of LAD artery ligation and cryoprobe are used to create cardiac injuries. Depending on the methods and timing of the injury, the neonatal heart will regenerate to a variable degree, with some amount of fibrosis. In adult mice, heart failure is induced by the administration of angiotensin II, L-NAME (NOS inhibitor), and HS water. After cessation of these agents, cardiac chamber size and function recover, along with increased vascularization and reduced fibrosis. In humans, LVAD implantation facilitates heart recovery, and the paired tissue obtained from LVAD implantation (pre-LVAD) and from the native heart at the time of transplantation (post-LVAD) are useful for studying the cellular and molecular events during heart failure recovery. Image created with BioRender.com. LAD: left anterior descending; NOS: nitric oxide synthase; HS: high salt; LVAD: left ventricular assist device; AII: angiotensin II; NOSi: NOS inhibitor; HFR: recovery from heart failure

of exceptionally high purity.[77] The iCM were grown in sheets of beating cardiomyocytes. In a murine model of MI (ligation of the left anterior descending coronary artery), the sheets of human iCM were applied to the surface of the ischemic myocardium. An improvement in heart function (by echocardiography) was likely due to the increased vascularization and reduced apoptosis observed in the murine myocardium in the vicinity of the cell therapy.

Another approach to regenerate the myocardium would be to generate induced cardiac progenitor cells (iCPC) from fibroblasts using specific transcriptional factors for cardiovascular lineage. Such iCPC are similar to early cardiac progenitors in the developing heart, which differentiate into cardiac myocytes as well as smooth muscle and endothelial cells.[78,79] Injection of such cells into the heart could theoretically regenerate the primary cells composing myocardial tissue, and may thus be a superior cell therapy to CMs alone. Yet another approach is to directly reprogram fibroblasts into CM in vivo using a CM lineage-directing cocktail or by exogenous expression of transcription factors.[80] A study from Cao et al. reported nine small compounds that in combination could induce functional CMs from fibroblasts.[81] A recent study from Zhou et al. used adeno-associated virus subtype 5 (AAV5) to deliver MYOCD and ASCL1 (Achaete-scute family bHLH transcription factor 1), and miR-133, to directly reprogram cardiac fibroblasts to CMs in rats post MI.[82] A single intramyocardial dose of the AAV5 therapy significantly improved heart recovery post-MI.

Several transcriptional factors are reported to be essential in mediating the direct reprogramming from fibroblast to CM, including GATA4 (GATA Binding Protein 4), MEF2C (myocyte-specific enhancer factor 2C), TBX5 (T-box transcription factor 5),[83] MESP1 (Mesoderm Posterior BHLH Transcription Factor 1), MYOCD (myocardin),[84,85] EZH2 (enhancer of zeste homolog 2),[86] and TBX20 (T-box transcription factor 20).[87] Investigators have used different combinations of these transcription factors, typically delivered by viral vectors, to achieve reprogramming of fibroblasts to CMs in vitro. Alternatively, small molecules or miRNA that can increase the expression of cardiac transcription factors also can induce reprogramming of fibroblasts to cardiac myocytes. Such reprogramming is of low efficiency, and the cardiac myocytes that are derived from this reprogramming are not electrophysiologically mature. Fibroblasts that are reprogrammed to CMs ex vivo must be transplanted into the heart, generally in a hostile environment characterized by ischemia and/or inflammation. An alternate approach is to deliver such reprogramming factors directly to the injured myocardium in order to reprogram resident fibroblasts into cardiac myocytes. Of interest, the induced cardiac myocytes generated by in vivo reprogramming appear to be more mature in their contractile and electrophysiological properties. However, the reprogramming is not highly efficient nor effective in the hostile environment of myocardial ischemia. In addition, cardiac arrhythmias could be promoted by incomplete reprogramming of the cells, or due to their dysfunction in a hostile environment.[88]

Another approach to cardiovascular repair is to ablate cells that may be contributing to disease processes. In seminal work from Rurik and colleagues, an in vivo CAR-T strategy was applied to a murine model of cardiac fibrosis. They used CD5-targeted lipid nanoparticles to transfect T-cells with a chimeric antigen receptor directed at activated cardiac myofibroblasts. The treatment was shown to selectively ablate fibroblast activation protein expressing fibrotic cells,[89] reduce cardiac fibrosis, and improve cardiac function.

Endothelial cells compose one of the largest non-myocyte cell populations in the heart[90] and play a key role in tissue repair.[91] Mesenchymal to endothelial cell transition (MEndoT) could expand the microvasculature and improve perfusion, and by doing so play a role in cardiac regeneration. However, the role of MEndoT in endothelial cell repopulation[92] after MI is controversial. One paper from Ubil et al. used Col1a2-CreERT: R26R-tdTomato mice fibroblast cell lineage tracing mice and observed the contribution of the Col1a2+ lineage cells to endothelial VE-Cadherin+ endothelial cells.[92] However, another work using more extensive lineage tracing studies reported contrary results showing that the preexisting endothelial cells, but not fibroblasts, modulate the neovascularization after MI.[93]

Whereas the role of MEndoT in recovery from MI is controversial, more evidence suggests that this process plays a role in other models of HF. In a transverse aortic constriction-induced cardiac hypertrophy model, MEndoT-originated cells appear to contribute to the neovascularization response.[94] In another model of ischemic disease (murine hindlimb ischemia), lineage tracing and single-cell transcriptional studies clearly show that a subset of fibroblasts undergoes MEndoT to contribute to revascularization of the limb.[95] In this case, the transdifferentiation of fibroblasts to endothelial cells is dependent upon inflammatory signaling and a metabolic switch.[62,95-98] We have reported that a metabolic switch from oxidative phosphorylation to glycolysis is required for angiogenic transdifferentiation.[99] This Warburg-like effect is associated with the upregulation of citrate synthesis in the mitochondria and its export to the nucleus. There, it is converted to acetyl-CoA to support histone acetylation and increased DNA accessibility, which facilitates cell fate transitions such as MEndoT. Harnessing endogenous MEndoT capacity could be a potential strategy to enhance tissue recovery in cardiovascular diseases.[100, 101]

CONCLUSION

Observations in our patients and animal models convincingly show that myocardial regeneration and myocardial recovery are possible in heart failure. Insights into the mechanisms underlying regeneration and recovery will lead to new pharmacological, cellular, and/or molecular therapies for heart failure.

KEY POINTS

- Myocardial recovery is characterized by a return toward normal structure and function of the heart after an injury.
- Myocardial regeneration is a crucial process that can facilitate the recovery of heart muscle.
- Preclinical mouse models and iPSC-based cellular reprogramming and engineered heart tissue are valuable tools to study the mechanisms of cardiovascular regeneration.
- Mesenchymal to endothelial transition involve critical chromatin reconfiguration mediated by epigenetic and metabolic regulations, representing a promising mechanism for cardiovascular regeneration.

COMPETING INTERESTS

Drs. Cooke and Lai have invention disclosures related to vascular regeneration that are assigned to Houston Methodist Hospital.

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