Recent Developments in Heart Failure

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Despite significant advances in cardiovascular medicine during the late 20th century, heart failure (HF) remains a leading cause of death in the United States and much of the rest of the world. Although improvements in acute management of cardiovascular disease have reduced death rates, efforts to halt the inexorable deterioration are largely futile. The current clinical approach focuses on disease management rather than curing HF because there is presently no cure.1 Primary treatment consists of angiotensin-converting enzyme inhibitors, β-blockers, and mineralocorticoids antagonists. And, although a new class of agents (ie, neprilysin inhibitor) has shown promise in a phase 3 clinical trial,2 collectively, these drugs only delay disease progression and death caused by HF. Given the general stagnation in the progress of clinical treatment of HF, we must undertake more daring and high-risk preclinical studies to achieve the collective dream of curing HF. This developments will highlight some recent progress in understanding the pathobiology of HF and advances in conceptual approaches for future treatments. The goal is to focus the readers’ attention on some of the more exciting and daring areas of cardiovascular research, which will likely dictate advances in the 21st century.

The central element of HF relates to the heart’s inability to pump sufficient blood to meet the metabolic demands of the body. Although various factors can contribute to such a defect, myocardial infarction (MI) is the most frequent cause of HF. After an infarction, the significant loss of cardiomyocytes is replaced with akinetic scar tissue, rather than contracting cardiac myocytes. Such wound healing satisfies the short-term goal of retaining ventricular integrity; however, the chronic implications include progressive fibrosis, stiffness, and dilation of the ventricle. Thus, improving mechanical performance and limiting remodeling represent 2 key areas to address in the failing heart.

Defects in Ion Handling
The basic contractile function of the heart is centrally regulated by ion exchange; in particular, the entry and exit of sodium and calcium, and propagation of action potentials. Although one could argue that elevated calcium during HF could augment cardiac function,3 elevated Ca²⁺ can be detrimental and can lead to the development of arrhythmias, hypertrophy, and apoptosis.4,5 More detailed discussion of calcium handling during HF can be found in a recent review.6 Of course, Na⁺/K⁺ ATPase, the primary ionic regulator in cardiomyocytes, has a long history as a target in HF (remember cardiac glycosides?). The familiar Na⁺/K⁺ ATPase has 2 subunits (α1 and α2), which can couple with a sodium-calcium exchanger in T tubules. Moreover, inhibition of the α2 isoform can increase calcium transients, indicating a possible link between Na⁺/K⁺ ATPase α2 and sodium-calcium exchanger. Correll et al7 recently examined the contribution of Na⁺/K⁺ ATPase α2 in regulation of disease progression.

In addition to changes in cation handling, structural remodeling is a key manifestation of cardiac dysfunction. The sarcoplasmic reticulum undergoes structural rearrangement in HF, and T tubules become swollen and progressively lose longitudinal branching.8 Such structural modifications have the potential to support abnormal calcium transients. Cardiac resynchronization therapy seems to correct structural changes attributed to dysynchronous HF, including disorganization of the T-tubule network and spatial relationship with ryanodine receptors.9

Inflammation and Remodeling
The induction of the inflammatory response is a critical step in mediating cardiac repair after MI. Robust infiltration of leukocytes mediates removal of necrotic cardiomycocytes and initiates wound healing. Recruitment of these inflammatory...
cells results from release of chemoattractants from damaged and dying myocardium. These cells become recruited to both infarcted and noninfarcted areas. The inflammatory response also helps mediate extracellular matrix synthesis through promoting fibroblast activation, extracellular matrix degradation, and altering matrix metalloproteinase (MMP) activity; however, chronic inflammation results in exacerbation of cardiomyocyte damage and cardiac dysfunction through adverse remodeling.10 Thus, the regulation of the inflammatory response and its mediators may provide new therapeutic targets in HF.

Ischemic cardiomyocytes release ATP, which can serve as a chemoattractant to recruit phagocytes to sites of inflammation to clear dead cells and debris.11 In addition, ATP can be released from neutrophils to guide other neutrophils to inflammatory sites. Extracellular ATP is rapidly dephosphorylated to ADP, AMP, and adenosine. These resultant products may play an integral role in modulating immune cell infiltration and cardiac healing/remodeling subsequent to ischemia/reperfusion. Recent studies12 have identified CD39 as an ecto-5'-nucleotidase responsible for the hydrolysis of ATP. Ecto-5'-nucleotidase (CD73) further hydrolyzes AMP to adenosine. Adenosine can subsequently induce both pro- and anti-inflammatory responses. Immune cells in the uninfarcted heart exhibit marked levels of CD39 and lack CD73; however, 3 days after I/R invading leukocytes exhibited significant upregulation of CD73.

Post-MI MMP activity increases in response to MI. Activation of MMPs leads to degradation of myocardial matrix and cardiac remodeling, and pharmacological inhibition of MMPs has demonstrated attenuation of left ventricular (LV) dilatation.13,14 In addition to MMPs, the heart also expresses tissue inhibitors of matrix metalloproteinases, whose expression is actually reduced after MI. Thus, our general understanding has held that a relative imbalance exists between MMPs and tissue inhibitors of matrix metalloproteinases. And, although recent insights derived from cardiac expression of tissue inhibitors of matrix metalloproteinase-4 demonstrates this idea clearly,15 not all MMPs mediate maladaptive remodeling. MMP-28 seems to be necessary for proadapptive remodeling.16 MMP-28 is expressed in cardiomyocytes in normal conditions; however, after MI, macrophages become a prominent source of MMP-28.16 Loss of MMP-28 leads to adverse LV remodeling and dysfunction, which is accompanied by increased death and rates of ventricular rupture.16 When the phenotype of the macrophages was examined, it seemed that both proinflammatory factors and M2 macrophage polarization were reduced with MMP-28 deletion. In addition, extracellular matrix deposition and cross-linking, and myofibroblast numbers, were all reduced in MMP-28 knockout mice.16

Clearly, macrophages play an important role in postinfarct wound healing, in part, through transition from M1 to M2 phenotype to reduce inflammation and mediate fibrosis. The necessity of macrophages in wound healing is even more evident in the neonatal heart. Macrophages play a pivotal role in cardiac regeneration and neoangiogenesis after myocardial injury.17 Thus, their use in mediating cardiac remodeling in the adult heart should be further explored. To this end, several elegant studies were published addressing primarily the role of macrophages in HF, and secondarily other aspects of inflammation. Ismahil et al18 developed the novel hypothesis that post-MI alterations of splenic function contribute to LV remodeling. In their study, they found that splenectomy blocked postinfarct LV remodeling, whereas reconstitution of naïve mice with HF-derived macrophages largely recapitulated LV remodeling. The origin of cardiac macrophages has been somewhat enigmatic; however, recent discoveries indicate that whereas homeostatic maintenance of cardiac macrophages occurs via proliferation of existing cardiac macrophages, bone marrow–derived monocytes contribute to postinfarct cardiac macrophages.19 Another question to be answered is what regulates the distribution Ly-6C^high (inflammatory) and Ly-6C^low (reparative) monocytes? A study from Hilgendorf et al20 addressed this important issue and found that Nr4a1 (nuclear receptor subfamily 4) expression was associated with suppression of inflammation, and deletion of Nr4a1 promoted adverse cardiac remodeling. Of course, macrophages are not solo actors in postinfarct inflammation; T lymphocytes may also exert critical regulatory effects on cardiac inflammation. Ablation of Treg cells before MI exacerbates inflammation, promotes M1 macrophage polarization, and depresses cardiac function in the failing heart.21

**Regulation of Cardiac Hypertrophy**

After cardiac injury, compensatory mechanisms, such as cardiac hypertrophy, maintain cardiac function. Cardiac hypertrophy serves primarily as an adaptive response to increased workload; however, chronically, hypertrophy is associated with increased interstitial fibrosis, apoptosis, and eventually HF. Hypertrophic growth requires gene regulation at multiple levels: epigenetic, transcriptional, post-transcriptional, and translational regulation. Regulation of hypertrophy in HF, especially the induction of the fetal gene program, has been studied extensively; however, new regulators have been identified, and seemingly complete stories22 have written new chapters.23

For example, G-protein–coupled receptors that result in the activation of Gq, and its downstream effects stimulate hypertrophy. Among these downstream effectors are histone deacetylases (HDACs), which normally suppress expression of hypertrophic genes. Class II HDACs, including HDAC4 and HDAC5, interact with key transcription factors that mediate hypertrophy including nuclear factor of activated T cells and myocyte enhancer factor-2 and inhibit their activity through histone deacylation. Yet, hypertrophic stimuli can activate HDAC kinases, such as protein kinase D, CamKII (Ca2+/calmodulin-dependent protein kinase II), and the recently discovered G-protein–coupled receptor kinase 5, which result in the phosphorylation and cytoplasmic translocation of class II HDACs and removal of their inhibitory effect on hypertrophic transcription factors. G-protein–coupled receptor kinase 5 overexpression promotes nuclear factor of activated T cell–induced activation of hypertrophic gene transcription, whereas G-protein–coupled receptor kinase 5 deficiency limits nuclear factor of activated T cell activation during pressure overload.24 Thus, limiting G-protein–coupled receptor kinase 5 expression may protect against maladaptive cardiac growth and HF development.
In addition to HDAC kinases, oxidation of specific serine residues of class II HDAC can also result in their cytoplasmic translocation. Sources of oxidation include reactive oxygen species that naturally result from physiological and pathological processes. In particular, nicotinamide adenine dinucleotide phosphate oxidases are major sources of superoxide formation. Recently, nicotinamide adenine dinucleotide phosphate oxidase 4 has been shown to increase reactive oxygen species in response to hypertrophic stimuli, resulting in cysteine oxidation and nuclear export of HDAC4, a class II HDAC. Similarly, deletion of nicotinamide adenine dinucleotide phosphate oxidase 4 attenuates HDAC4 oxidation and cardiac hypertrophy 2 weeks after pressure overload. Clearly, HADACs play an important role in suppressing hypertrophy, and regulating their activity may regulate the transition to decompensated HF.

Controlling the intensity and duration of hypertrophic signaling may provide therapeutic benefit in HF. Interestingly, the Sussman group may have found a novel target for the regulation of cardiac hypertrophy in Pin1. Pin1, a proline-directed isomerase extensively studied in cancer, where it regulates proliferation, cell survival, lineage commitment, and aging, now appears to orchestrate cardiac hypertrophy. Pin1 is upregulated after pressure overload, and loss of Pin1 limits cardiomyocyte hypertrophy through the inhibition of Akt and mitogen-activated protein kinase kinase (MEK) activation. Pin1 overexpression preserves cardiac function after pressure overload, possibly through inhibition of MEK but not of Akt. Because attenuation of the hypertrophic response was attributed to both overexpression and loss of Pin1, Toko et al surmised that Pin1 operates within a restricted range. Thus, Pin1 seems to facilitate an appropriate hypertrophic response through regulation of intensity and duration of hypertrophic signaling.

Preserving cardiac function is the ultimate goal, and technological advances in mechanical circulatory support have led to the development of left ventricular assist devices (LVAD). These devices serve as a last resort therapeutic option for patients with end-stage HF to provide a bridge to transplantation. Considering the universal shortage of donor organs, LVADs offer decreased mortality and morbidity for those on a waiting list. After 30 days of LVAD implementation, patients exhibit recovery of ejection fraction; however, such improvement often regresses to the pre-LVAD level on withdrawal of LVAD. As expected, cardiac tissue examined pre and post LVAD demonstrates reduced myocyte size and fibrosis without an obligatory improvement in function. Such findings provide some limited promise for LVADs and re-emphasize the bidirectional nature of myocardial remodeling. Thus, understanding the underlying mechanisms may guide our ability to mend the failing heart.

**Gene/Molecular Therapy**

Because HF is not a single loss-of-function genetic abnormality, fine-tuning gene expression may represent another feasible avenue via micro-RNAs (miRs). These small, noncoding RNAs are responsible for genetic regulation at the post-transcriptional level. MiRs can directly modulate cardiac transcription and indirectly regulate other miRs. Thousands of miRs have already been identified and many regulate cardiac development, pathological remodeling, and cardiomyocyte hypertrophy. For example, miR-25, which is a potent inhibitor of sarcoplasmic reticulum Ca2+ ATPase (SERCA2a), can be blocked (via antago-miR) to improve contractility during HF. With the confirmation that miRs are present in patients’ sera after MI, miRs may even represent under investigated biomarkers. Other more recently discovered noncoding RNAs, such as long noncoding (Inc) RNAs, may present new approaches to manipulate the hypertrophic heart.

Although once heralded as a definitive treatment for mono- genetic disorders, gene therapy has been slow to gain traction in cardiovascular medicine; however, several groups have recently reinvigorated interest in gene therapy to mitigate HF. Defective calcium handling is a key aspect of HF. Of the multiple regulators of calcium handling in HF, SERCA2 has received significant attention because of its primary role in calcium reuptake to the sarcoplasmic reticulum. Indeed, SERCA2’s activity is diminished in the failing heart, and adenosinal administration of SERCA2 antisense to failing cardiomyocytes improves contractility in various animal models of HF. The resulting clinical trial, Calcium Up-Regulation by Percutaneous Administration of Gene Therapy In Cardiac Disease (CUPID), demonstrated safety and efficacy of intracoronary infusion of recombinant AAV1 (adeno-associated virus serotype 1)/SERCA2a. Through 3 years of follow up, gene therapy caused no adverse events, even though the SERCA2a transgene was present in patients ≤31 months post transfusion. Gene therapy seems to be a feasible, clinical therapeutic option.

Ultimately, although preserving and enhancing cardiomyocyte function serves to potentiate the adverse effects of the failing heart, the need to address the loss of cardiomyocytes and their limited renewal still looms. Replacing the cardiomyocyte pool seems to be the limiting factor in mediating cardiovascular disease because most treatments are geared toward maintaining cardiomyocyte survival and function. Recent studies demonstrate the ability to reprogram cells into cardiomyocyte-like cells. Gene transfer of 4 cardiac factors, GATA4 (GATA binding protein 4), HAND2 (heart and neural crest derivatives-expressed protein 2), myocyte enhancer factor-2C, and TBX5 (T-box transcription factor 5), into fibroblasts cooperatively induces transformation into beating cardiomyocyte-like cells. In addition, gene transfer of these factors after MI ameliorates cardiac function and attenuates fibrosis. It remains to be seen whether reprogramming resident fibroblasts would provide clear clinical benefit. Subpopulations of resident cardiac fibroblasts do indeed have a cardiac-specific gene expression profile and may be primed for transdifferentiation; however, cardiac fibroblasts, in general, do not contribute substantially to myocardial regeneration after injury.

The key to genetic regulation of neocardiomyogenesis may revolve around regulation of the cardiomyocyte cell cycle to induce cardiomyocyte proliferation. Adult cardiomyocytes are terminally differentiated and have likely exited the cell cycle, diminishing any significant capacity for proliferation. Recently, Chen et al studied the miR-17 to miR-92 cluster,
a human oncogene that induces proliferation in the heart. Deletion of this cluster from embryonic and postnatal hearts reduced cardiomyocyte proliferation, and in vitro overexpression of the miR-17 to miR-19 cluster seems sufficient to induce cardiomyocyte proliferation. Furthermore, overexpression of this cluster after MI modestly improved cardiac function, decreased scar formation, and induced cardiomyocyte proliferation.50 Indeed, others found the let-7 miR family is important in shifting the metabolism of stem cells toward that of adult cardiomyocytes.50 Elucidating the molecular signaling mediated by this cluster may provide necessary molecular targets to mediate robust de novo cardiomyocyte formation in the context of cardiac necrosis.

**Cell Therapy**

The heart was thought to be a postmitotic organ with limited (if any) capacity for regeneration; however, discovery of putative stem/progenitor cells in the heart ushered in a relative renaissance in cardiovascular research. It is now accepted that zebrafish can regenerate myocardium without scar formation,51 and this regenerative capacity is present in neonatal mice (within 7 days), but disappears with age.52 This process seems to involve macrophages.17 Thus, the mammalian heart contains the genetic capacity to increase the number of cardiomyocytes after injury. Yet, the effective regeneration in the adult mammalian heart is negligible. Several groups are working to identify the molecular switches to effect endogenous cardiomyogenesis. Neuregulin, which was thought to improve cardiomyocyte survival if not a limited degree of regeneration by the host myocardium. Given the initial promise of replacing completely the heart’s lost contractile units, we still have a long road to fulfill that dream. Large clinical trials will hopefully provide definitive insight on the efficacy of cell therapy. Although several recently completed trials are varied in cell type and outcomes, they all exhibit limited adverse effects in patients indicating a suitable vehicle for further experimentation; that is, at minimum, cell therapy seems to be safe.

There is a race to find the most effective cell type to mediate cardiac regeneration and, eventually, improve clinical outcomes. The race to find the most therapeutic cell requires stringent and thorough examination of the regenerative potential and appropriate product control. There are obstacles that still need to be surmounted, including developing high throughput methods for testing the cells. Purifying, selecting, and injecting potential cardiac progenitors to measure functional outcomes after HF without properly addressing the cells’ functional and regenerative capacity is a timely and costly endeavor. In addition, there are a multitude of cell markers that may be attributable to therapeutic potential. Studying the efficacy of these cells in high throughput in vitro settings may be beneficial in the future of the field.

Although some of the cells used for cell therapy may indeed be unique subsets of fibroblasts, which many have speculated (and certainly has conceptual underpinnings47), they seem to be collectively effective in the hands of numerous investigators. This is an exciting time for the field of cell therapy.

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**Disclosures**

None.

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