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Gene therapy for beating heart failure

Gene therapy for cardiomyocytes, a heart beat away

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Koch and colleagues (*Circulation* 2009; **113**: 89)[1] may have re-ignited the interest of cardiologists in gene therapy. They have shown a healthy, viable pipeline of therapeutics with data that shows a recovery strategy for heart failure.[1] Their clinically relevant data were gathered using a recombinant Adeno-associated virus (AAV) to rescue loss of contractility in the myocardium. The team also observed long-term benefits comparable with using a β-blocker, but with potentially more advantages. The convincing results of this carefully designed and executed study provide a strong impetus to undertake further preclinical evaluation in larger, more anatomically relevant models.

Heart failure (HF) is one of the main causes of morbidity and mortality in the developed world. The prognosis of a patient with chronic NYHA (New York Heart Association) class IV heart failure is bleaker than for a patient with any type of malignancy, except carcinomas of the lung and pancreas.[2] A defining characteristic of the disease is impaired ventricular function, which causes inadequate systemic blood flow, and the body compensates with changes, such as cardiac hypertrophy, increased sympathetic activity and increased activation of the renin–angiotensin system. Another characteristic of HF is systolic dysfunction, which involves reduced left ventricle contractility and a lowered ejection fraction.

The signaling pathway of the β-adrenergic receptor (β-AR), as described by Rengo *et al.*,[1] plays a pivotal role in the regulation of myocardial force, rate and relaxation. Dysregulation of the pathway has been shown to be a hallmark of HF, and antagonism of the receptor with β-blockers, such as metoprolol, has recently become a standard adjunct therapy to treat the disease. Earlier studies have focused on the dynamic interactions between the neurohormonal systems and molecular pathways that underlie myocardial contractility and heart rate,[3,4] and our understanding of the pathway has benefited significantly from this earlier work.

There are several genetic strategies to modify the underlying disease processes. These include protecting the myocardium by enhanced antioxidant gene expression, the rescue of failing myocardium by enhanced proangiogenic gene expression, and the recovery of contractile function by β-AR signaling.[5] Gene delivery interventions have reduced diastolic calcium levels in the cytosol by overexpressing cardiac Ca^{2+} ATPase of the sarcoplasmic reticulum (SERCA2a), increasing the phospholamban mutated proteins, reducing the endogeneous phospholamban and increasing the protein phosphatase-1 inhibitor-1 activity. They have been used to normalize β-adrenergic signaling by overexpressing β-adrenergic type-2 receptors and to reduce the G-protein-coupled receptor kinase 2 activity by the overexpression of the inhibitory peptide, β-adrenergic receptor kinase (βARKct, Figure 1).

The targeting of calcium levels with intracoronary AAV1-SERCA2a safely completed phase I and is currently in phase II clinical trial.[6,7] In addition, a treatment designed to deliver a constitutively active version of inhibitor-1 is in preclinical development (author disclosure). The study by Rengo *et al.*[1] provides momentum for further preclinical development of a βARKct gene delivery approach, which has the potential to resolve β-AR downregulation and desensitization of issues associated with HF.

Earlier studies of βARKct gene delivery[4] were limited by the use of a vector with high-level gene expression for only a short period of time. As myocardium remodeling and the associated hormonal regulation happens over a longer time, meaningful clinical conclusions drawn from βARKct overexpression were limited. Koch and colleagues optimized the AAV-based delivery to the myocardium to provide stable, long-term transgene expression.[1] This allowed contractile function changes and neurohormonal signaling normalization to be examined over the clinically relevant time period of 3 months.

Elevated levels of G-protein-coupled receptor kinase 2 are characteristic of a failing myocardium, and therefore they used an AAV6 vector to express the peptide βARKct, which had earlier been shown to inhibit G-protein-coupled receptor kinase 2 activity.[4] The treatment reduced the desensitizing effect of G-protein-coupled receptor kinase 2 on the β-AR, the receptor that controls the level of contractile force, heart rate and relaxation. The βARKct peptide, thus acted as an upstream effector to normalize the regulation of myocardial function.

In addition, Koch and colleagues included a β-blocker control group and tested a combination treatment of gene transfer with β-blocker. This work with an existing pharmacological treatment has helped to establish the therapeutic potential of their approach. Although β-blockers alone help prevent HF, the combination treatment went a step further by showing potential for recovery of function in sufferers.

Significant development work is required before this genetic approach to HF treatment is ready for clinical testing. One critical element will be to evaluate the dose-response relationship in a large animal model. Earlier studies of β2-AR receptor overexpression in a transgenic model generated unexpected results, including cardiomyopathy, postulated to be caused by extremely high levels of expression.[3] The therapeutic window must, therefore, be well defined for βARKct delivery to be successful.

There is also the potential for off-target downstream responses that need evaluation. Any intervention that increases levels of intracellular cyclic adenosine mono-phosphate (such as expression of βARKct) has the potential to cause ventricular arrhythmias and this adverse

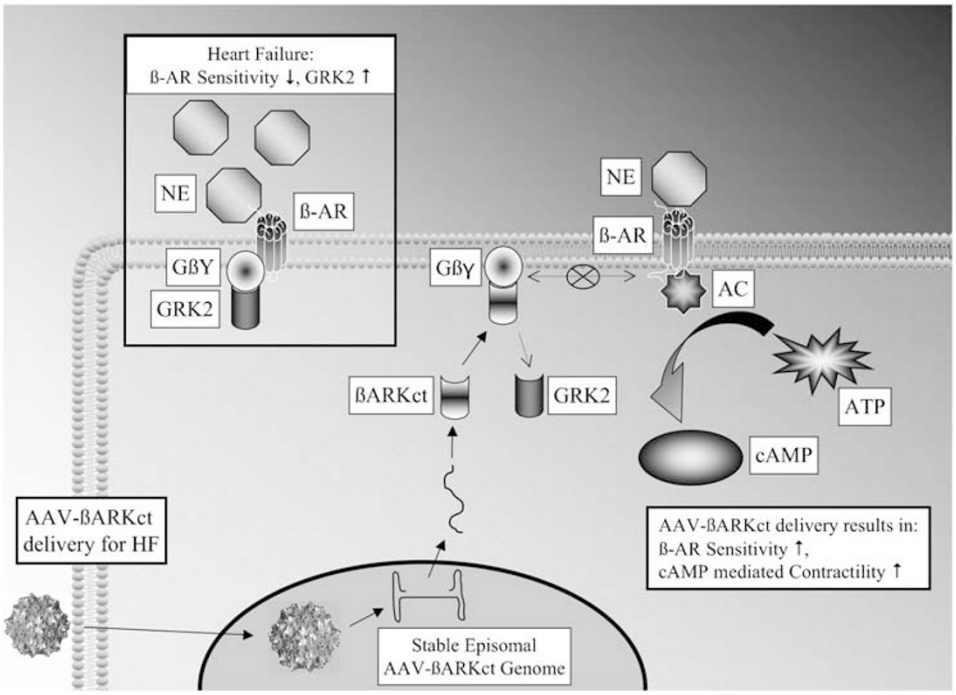

Figure 1 AAV-βARKct rescues β-adrenergic signaling in heart failure. Elevated GRK2 in heart failure is involved in β-AR desensitization and dysregulation of the sympathetic nervous system. AAV-βARKct recovers β-AR function leading to improved myocardial contractility. AAV, Adeno-associated virus; ATP, adenosine tri-phosphate; β-AR, β-adrenergic Receptor; βARKct, constitutive truncated β-adrenergic receptor kinase 1; GβY, βY-subunit of heterotrimeric G protein; cAMP, cyclic adenosine mono-phosphate; NE, norepinephrine; GRK2, G-protein coupled receptor kinase 2; HF, heart failure.

outcome should be monitored in future studies.

The Koch group have generated a robust proof of concept data-set supporting βARKct gene delivery for heart failure.[1,4] Convincing biological activity and toxicology studies in a large model are now required to support this approach to advance into the clinical arena.

Conflict of interest

Samulski holds several patents that are licensed to biotech and pharmaceutical companies, and Samulski and McPhee declare a financial holding in Asklepios BioPharmaceutical Inc. and affiliates. ■

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