HHS Public Access

Author manuscript

Mol Ther. Author manuscript; available in PMC 2016 May 03.

Published in final edited form as:

Mol Ther. 2008 June ; 16(6): 1002–1004. doi:10.1038/mt.2008.89.

SERCA2a Gene Therapy for Heart Failure: Ready for Primetime?

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Cardiovascular disease has emerged as one of the leading causes of morbidity and mortality in recent years. Despite considerable progress in managing the disease, we still face the daunting challenge of developing therapeutic interventions to effectively treat heart failure and improve heart function. Although conventional pharmacologic therapy has been quite successful in relieving symptoms, there is no cure for heart failure.[1] However, several experimental studies have demonstrated that gene therapy could be an effective option to treat the failing myocardium.[2–6] Many of these studies have focused on the calcium (Ca^{2+})-handling proteins of the sarcoplasmic reticulum in an effort to improving calcium cycling in the diseased heart.[2,5–8]

There have been promising animal studies, but the field has met with numerous hurdles in translating gene therapy to human patients. These include inefficient gene delivery systems, uncontrolled levels of target gene expression, limitations on the size of the therapeutic gene, severe host immune responses, and defining the time of administration. Designing a vector that not only delivers the gene of interest efficiently but does so without triggering any undesirable side effects, such as inflammatory responses, continues to be a major obstacle. Therefore recent efforts have been focused on developing viral vectors that are less immunogenic but at the same time can integrate into the host genome and continue to express the protein for a prolonged period. One such popular vector is the lentiviral vector, because it can easily infect nonreplicating, terminally differentiated cells and can also integrate into the genome without the need for cell division. In this issue, Niwano *et al*.[9] report that they have used this vector very successfully to deliver the sarcoplasmic reticulum Ca^{2+} ATPase (*SERCA2a*) gene into the cardiac myocardium to rescue heart failure.

Several pathologic alterations that occur during heart failure have been targets for gene therapy, but restoring Ca^{2+} transport has received tremendous attention in the past few years. There has been particular emphasis on calcium-transport genes as candidates for gene therapy, including *SERCA2a*, phospholamban (*PLB*), ryanodine receptor (*RyR2*), and the sodium-calcium exchanger (*NCX*) (Figure 1). Among the major sarcoplasmic reticulum proteins that have been investigated, SER-CA has proven a very promising candidate because its expression and activity are decreased in a wide variety of pathologic conditions in heart failure.[10–12] In addition, a decrease in SERCA pump level and sarcoplasmic reticulum Ca^{2+} transport is well correlated with negative force frequency seen in failing

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hearts.[13–15] Results from studies using cell systems and rodent models have presented a clear proof of concept that increasing SERCA pump levels can improve cardiac muscle function.[3,16,17]

Del Monte *et al*. first showed that over-expression of SERCA2a in failing human ventricular myocytes isolated from patients with end-stage heart failure can increase SERCA pump activity and enhance contraction and relaxation velocity.[17] These studies led to the development of *in vivo* gene transfer using an elegant catheter-based technique to introduce *SERCA2a* into the myocardium.[2–4,18–20] Adenoviral-mediated *SERCA2a* gene transfer in a rat model of pressure-overload hypertrophy (in which SERCA2a levels were decreased and severe contractile dysfunction was evident) restored both systolic and diastolic dysfunction to normal levels. Restoration of SERCA2a levels decreased left ventricular size and restored the slope of the end-diastolic pressure–dimension relationship to control levels.[20] Interestingly, overexpression of SERCA2a in failing heart restored and normalized the levels of phosphocreatine and ATP and suggested that normalizing Ca^{2+} transport would improve energetics.[3,20] Furthermore, adenoviral-mediated *SERCA2a* gene transfer into the infarcted myocardium significantly decreased ventricular arrhythmias, reduced infarct size, and improved wall thickening in the anterior wall.[8] An increase in Ca^{2+} transport and a decrease in diastolic Ca^{2+} and better handling of intracellular ions during the rush of reperfusion should result in improved survival of the cardiomyocytes. Improving Ca^{2+} transport by *SERCA2a* gene transfer is therefore beneficial for maintaining cardiac inotropy and for preventing the pathologic effects of Ca^{2+} overload. Many of the earlier studies used adenoviral gene transfer to deliver target genes.[3,5,7,8,19,20] But a major disadvantage of adenoviral vectors lies in the activation of the host immune system and potential destruction of cardiac myocytes when applied *in vivo*.

Inflammatory responses induced by adenoviral particles can be very strong and fatal to the recipient, as reported in initial human trials. New classes of vectors that provide an alternative to the adenovirus include recombinant adeno-associated virus (AAV) and lentiviral vectors. The recombinant AAV vectors can also infect nondividing cells; they are less immunogenic and do not contain viral genes, but they can accommodate only up to 4.8 kilobases of DNA, somewhat limiting their use for larger genes. On the other hand, lentiviral vectors are becoming increasingly popular because they can easily infect nonreplicating, terminally differentiated cells and can incorporate into the genome without the need for cell division. Lentiviral vectors have also been increasingly popular for long-term stable gene expression in a variety of cells, including vascular smooth muscle cells and endothelial cells.[21]

In the new study reported in this issue, Niwano *et al*. infused a lentiviral vector containing the *SERCA2* gene into the rat heart by a hypothermic intracoronary delivery method 2 weeks after myocardial infarction (MI).[9] They have shown for the first time that the *SERCA2* gene can be targeted to the myocardium using lentiviral vectors and they have documented improved cardiac function in a rat model of ischemic cardiomyopathy. In addition, their study demonstrates that the therapy prevented geometrical left ventricular remodeling after MI and also improved the survival rate.

These data are significant in several respects. One is that they identify an efficient vector that is superior in many ways to the existing options. The lentiviral system used in this study is a third-generation vector with several safety features that are necessary for minimal production of replication-competent viruses. The data also demonstrate that *SERCA2* administration is significantly effective even 2 weeks after an MI episode, thereby offering a potentially translatable therapy. Third, the study shows that 6 months after transduction *SERCA2* gene transfer significantly prevented left ventricular dilation and improved systolic and diastolic function, resulting in reduction of mortality. These results are very promising in that the lentiviral vectors could be tailored to situations in which stable long-term transgene expression is needed, without the adverse effects of adenoviral vectors and multiple viral administrations. Such long-term interventions could present effective treatment options for both vascular and cardiac disease.

Exciting findings such as those from Niwano *et al.*[9] take us one step closer to achieving what has been pursued for more than two decades. This study has identified a better tool for delivering the gene and tested the possibility of delayed gene delivery following MI. However, potential complications, including electrical heterogeneity resulting from uneven expression of the target gene, will need to be rigorously tested and optimized. Future research must identify tissue-specific gene delivery and expression systems to ensure targeted integration of the gene as well as its controlled expression. As technology continues to improve, gene therapy is no longer at an experimental stage to treat heart disease, because the translation of these results into tangible clinical therapy is already in progress. At least two clinical trials using *SERCA2* gene transfer are in preparation: a phase I, randomized double-blinded, placebo-controlled study using AAV1-*SERCA2a* (Mydicar; Celladon Corporation, La Jolla, CA) in patients with congestive heart failure, and a phase I study using AAV6-*SERCA2a* to evaluate efficacy and safety in ischemic patients undergoing left ventricular assist placement.[2] With further development of improved delivery methods and advanced viral vectors, *SERCA* gene therapy may not be far from reality.

Acknowledgments

We thank Robert M. Frederickson, Editor of *Molecular Therapy*, for his input and valuable comments. MP is supported by RO1 HL 08855 and R01 HL-64140-06.

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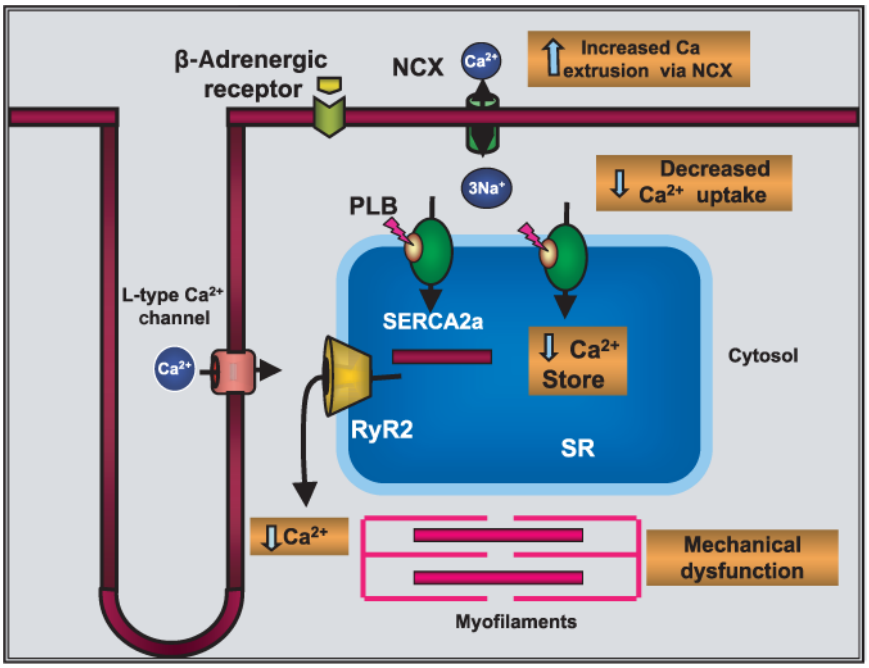

Figure 1. Altered Ca^{2+} transport in heart failure and targets for gene therapy

NCX, sodium-calcium exchanger; PLB, phospholamban; RyR2, ryanodine receptor; SR, sarcoplasmic reticulum.