Commentary: Doubling down on adeno-associated viruses for cardiac gene therapy

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After myocardial infarction, maladaptive changes within individual cardiomyocytes include a progressive cellular energy deficit, increased oxidative stress, disturbed ion handling, and disordered contractile machinery. Calcium handling is an energy-consuming and tightly regulated process at the center of this cascade and improper subcellular localization can propagate contractile failure. S100A1 appears to play an essential role in this system as a calcium sensor with the ability to regulate adenosine triphosphate (ATP)-dependent reuptake of calcium by the sarcoplasmic reticulum, as well as the production of ATP by mitochondria. Because patients with heart failure exhibit reduced levels, there has been substantial interest in developing S100A1 as a therapeutic target. Disease states driven by insufficient amounts of specific proteins are alluring targets for gene therapy, because the cell’s own transcriptional machinery can be utilized to efficiently produce large quantities; however, the delivery vector must also be chosen carefully to ensure appropriate location and persistence of overexpression while minimizing off-target expression and toxicity. Unlike gene therapy for angiogenesis or direct cardiac reprogramming, in which transient expression is acceptable or potentially desirable, transgenic expression needs to be persistent for targets with proposed functional benefits in cardiomyocytes themselves. The sustained expression afforded by adeno-associated viruses (AAVs) has led to their steadily increasing adoption as recombinant vectors for gene therapy, with multiple groups modifying the viral capsid and genome for increased specificity or transduction efficiency.

In this issue of the Journal, Katz and colleagues present an extensive evaluation of transgenic S100A1 overexpression after myocardial infarction through local injection of a typical (single-stranded) AAV vector versus a modified AAV with a “self-complementary” genome, which bypasses a rate-limiting step in the translation of target proteins. Transgenic overexpression by either virus type persisted at 10 weeks after myocardial infarction and preserved cardiac function to a much greater degree than placebo, consistent with previous reports in small and large animals by this group and others. The self-complementary AAV group also demonstrated a higher concentration of S100A1 messenger RNA per cell at 10 weeks at an equivalent dose, suggesting that these viruses could permit lower doses in clinical usage. The current report of Katz and colleagues expands on earlier work by providing a detailed histologic and molecular characterization of the infarcted myocardium. Not only were infarct size and extent of fibrosis reduced in both groups with transgenic S100A1 overexpression, but damage to intracellular components within individual cardiomyocytes appeared to be largely ameliorated as well. Although Katz and colleagues used an acute infarction model, these findings suggest that benefits may extend to patients with contractile failure from chronic ischemic or other etiologies. The molecular mechanisms underlying the beneficial effects of S100A1 overexpression remain

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Disclosures: Authors have nothing to disclose with regard to commercial support.

Received for publication Oct 18, 2019; revisions received Oct 18, 2019; accepted for publication Oct 21, 2019; available ahead of print Dec 12, 2019.

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J Thorac Cardiovasc Surg 2020;159:1823-4
0022-5223/$36.00
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https://doi.org/10.1016/j.jtcvs.2019.10.111
to be fully elucidated and could potentially be explained by alterations in survival and functioning of cardiomyocytes or alternative cell types such as fibroblasts. These questions are compounded by the lack of detailed information on the function of the S100A1 protein itself, as noted by Katz and colleagues. This report adds to the expanding body of work covering this intriguing therapeutic target, as well as the interplay between viral vectors and resultant kinetics of transgene expression. Remaining open questions include the applicability of S100A1 overexpression to chronic disease states, optimal dosing levels, and the expected durability of benefit. The need for optimal dosing is reinforced by the relatively high levels of off-target expression seen in the liver in both viral groups, which reinforces that AAV9 may be cardiotropic but cannot be considered cardiospecific and that systemic risks cannot be ignored. These issues do not reduce the potential of this intriguing gene therapy target and vector combination, but they will need to be addressed to allow for proper planning and implementation of clinical investigations.

References