even be detrimental? Besides the cardiomyocytes, are other cardiac cells influenced by the induction of Anc80L65 vector? The study by Katz and colleagues\(^2\) includes empiric observations on a synthetic AAV gene transport; the rat hearts with Anc80L65 were aptly compared with another optional heart delivery means including AAV9 vector. The study reveals limitations of accepting the technology clinically, but it suggests that a sustainable gene therapy using Anc80L65 may replace the less precise AAV9 vector.

References

Commentary: Can the new synthetic adeno-associated virus vector deliver the promise of cardiac gene therapy?

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Katz and colleagues\(^1\) have reported the use of a synthetic adeno-associated virus (AAV) lineage clone, Anc80L65, and compared it with AAV9. They showed that transfer of reporter genes with Anc80L65 in rat cardiomyocytes and rat hearts was more efficient and robust than AAV9.\(^1\) This was not associated with off-target transfection in other organs, lymphocyte or neutrophil activation, alteration in inflammatory cytokines, or disturbance of cardiac function. These findings are consistent with favorable reports of Anc80 in gene therapy in the retina and the central nervous system.\(^2,3\) However, the optimal route of administration, whether intramyocardial or intracoronary, needs to be determined. Only a single vector dose was studied, and the optimal dosing and timing warrant further investigation.

In the past 5 years, several gene therapy products received approval for clinical use.\(^4\) However, the goal of therapeutic gene therapy in the heart remains elusive. Studies of cardiac gene therapy have focused mostly on 2 areas: therapeutic angiogenesis for coronary artery disease where conventional revascularization is not feasible and heart failure.

Notable examples of angiogenesis clinical trials include naked DNA plasmid encoding vascular endothelial growth factor A (VEGF-A) (EUROINJECT-1, NOGA Angiogenesis Revascularization Therapy: Assessment by Radiouclide Imaging [NORTHERN trial], Kuopio Angiogenesis...
Trial [KAT]),5-7 or encoding both fibroblast growth factor (FGF)-2 and VEGF-A (Intramyocardial Plasmid-Encoding Human Vascular Endothelial Growth Factor A165/Basic Fibroblast Growth Factor Therapy Using Percutaneous Transcatheater Approach in Patients With Refractory Coronary Artery Disease [VIF-CAD])8; adenoviral vectors with cDNA expressing VEGF-A (Randomized Evaluation of VEGF for Angiogenesis [REVASC], NOGA Delivery of VEGF for Angina [NOVA], KAT),7,9,10 or FGF4 (Angiogenic Gene Therapy [AGENT]).11 None of the plasmid trials showed major influence on clinical outcomes or symptoms, and REVASC failed to show objective improved perfusion; NOVA and AGENT were prematurely terminated.

In heart failure, the early Calcium Upregulation by Percutaneous Administration of Gene Therapy in Cardiac Diseases (CUPID) trials (AAV1 vector to transfer sarco/endoplasmic reticulum Ca2+-ATPase (SERCA) 2a DNA) were promising,12 but the follow-up Phase 2b CUPID 2 failed to improve clinical outcomes.13

Adenyl cyclase gene transfer improved left ventricular function and remodeling in failing heart in preclinical studies.14 However, the Phase 3 FLOURISH trial using adenoviral delivery of adenyl cyclase was terminated because of recruitment issues and reevaluation of strategy.15

The synthetic AAV Anc80L65 is a vector that shows promise in tackling a key hurdle in gene therapy, namely efficiency in gene delivery. However, gene transfer efficiency alone does not guarantee success of cardiac gene therapy. A limitation is the lack of suitable animal models in preclinical studies. A single intramyocardial injection reaches a much larger area in a rodent heart compared with a human heart.16 Patients being considered for gene therapy trials are in end-stage disease and often have multiple comorbidities, unlike the young healthy laboratory animals used in preclinical studies where the induced pathology is of short duration.17 Furthermore, with the realization of the complexity of vascularization process, where it is now known that several dozens of factors are involved in vessel formation, targeting 1 or 2 genes may not be the answer to generate functional blood vessels in angiogenesis.17

Preclinical work in the areas of modulation of gene expression in the heart using noncoding RNA therapeutics and gene editing for inherited cardiac diseases represent exciting new directions that may fulfill the promise of cardiac gene therapy in the future.17

References