Intramyocardial Injection of Serca2a-Expressing Lentivirus Improves Myocardial Function in Doxorubicin-Induced Heart Failure

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Conflicts of interest

• None
Heart Failure

- Up to 10% of people over 75 yrs
- CAD, HA, Valvular disease, cardiomyopathies
- Pharmacological, interventional and device therapies
- HF has a poor prognosis
  - Median survival 3-5 yrs
SERCA2a in cardiomyocyte contraction

Figure 2. Ca\(^{2+}\) handling proteins involved in Ca\(^{2+}\) movement.
SERCA2a as a HF target

- SERCA2a expression in heart failure
- SERCA2a Tg mice enhanced contractility
- SERCA2a gene transfer animal studies
- SERCA2a gene therapy clinical trials
Hypotheses

• Ultrasound-guided lentiviral SERCA2a injection is safe and feasible
• Leads to stable and robust gene expression in target cells
• Leads to improved left ventricular function in heart failure model
Doxorubicin Cardiomyopathy model
Methods

• Lentivirus: long-term expression large transgene capacity

Western blot: SERCA2 protein level correlates with the infection level of the HEK293T cells
Methods

• Mouse cardiomyopathy heart failure model
  – Induction by Doxorubicin i.p. 20 mg/kg
• 3 groups (LV-SERCA2a-GFP, LV-GFP, PBS)
• Ultrasound-guided intramyocardial injection into the anterior wall of the left ventricle
• Echo control at days 7 and 28
Results

• Intramyocardial injection was well tolerated
• Robust GFP expression in anterior wall of left ventricle
PCR
Echocardiography

change in ejection fraction d7 to d28
Echocardiography

change in ESV and EDV d7 to d28

SERCA2a  GFP  PBS

SERCA2a  GFP  PBS

ESV

EDV

SERCA2a  GFP  PBS

SERCA2a  GFP  PBS

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Conclusions

• Ultrasound-guided lentiviral SERCA2a injection is well tolerated and leads to robust gene expression in target cells
• Lentiviral SERCA2a overexpression leads to improved left ventricular function in doxorubicin heart failure model
• These results encourage further clinical development of LV-SERCA2a gene therapy
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