Cell-to-cell propagation of cell death induced by excess iron in cardiomyocytes

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Heart Disease Mortality

- Coronary Heart Disease (44%)
- Stroke (17%)
- Heart Failure (9%)
- High Blood Pressure (9%)
- Diseases of the Arteries (3%)
- Other (18%)

(Benjamin, E. J. et al., 2018 Circulation 137: e257)
LV Remodeling

POST-MI REMODELING

Acute Infarction → Infarct Zone Thinning & Elongation → Spherical Ventricular Dilation

Fibrous Scar → Increased Interstitial Collagen

Myocyte Hypertrophy

T2* in Cardiac MRI shows Iron Accumulation surrounding Myocardial Infarction

(Bulluck, H. et al., 2016 Circ Cardiovasc Imaging 9(10))
Stains of Hearts in Post-MI Patients
Cellular Iron Homeostasis and ROS Production

(Kobayashi, M. et al., 2018 Current Drug Targets)
Ferroptosis

(Kobayashi, M. et al., 2018 Current Drug Targets)
Excess Iron induces Cell Death in Mouse Cardiomyocytes

(Baba Y. et al., 2018 Am J Physiol Heart Circ Physiol 314: H659-H668)
Excess Iron-induced Cardiomyocyte Cell Death

(Baba Y. et al., 2018 Am J Physiol Heart Circ Physiol 314: H659-H668)
Objective

To demonstrate cell-to-cell propagation of cell death induced by excess iron in cardiomyocytes
Methods

• H9c2 cells cultured in 12-well plates containing DMEM with 10% FBS

• Negative control – DMEM

• Positive controls – DMEM with 50 ng/mL RSL-3 (ferroptosis inducer) or 20 uM H₂O₂ (nonspecific cell death inducer) for 3 hrs

• Experimental – DMEM with 5 mM, 10 mM, 20 mM, and 30 mM iron (III) citrate for 16 hrs

• Cell death was analyzed with Live/Dead Cell Viability Assay with fluorescent microscopy, 40X magnification
DMEM – Negative Control

RSL-3 (Ferroptosis Inducer)

H$_2$O$_2$ (Nonspecific Inducer)
5 mM Fe (III) citrate

10 mM Fe (III) citrate

20 mM Fe (III) citrate

30 mM Fe (III) citrate
Summary

- Treatment with ferroptosis inducers resulted in contiguous or “clustered” cell death

- Treatment with excess iron induced cell death with a clustered pattern in a dose-dependent manner
Conclusions

• Dose-dependent clustering of cell death suggests that excess iron can produce cell-to-cell propagation of cell death

• Differences in patterns of cell death suggest specific mechanisms that contribute to cardiomyocyte cell death

• Further understanding into the differences in these mechanisms of cell death may provide insight into treatment that can prevent adverse LV remodeling
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