Proteotoxicity and cardiac disease
Proteinopathy: A definition
Any disease caused by a malformed protein

**Desmin Related Myopathy (DRM):**
distal muscle weakness, wasting
- RCM, HCM or DCM, bundle block
- linked to desmin or α-B-crystallin mutations
HF (HCM) human heart stained with anti-oligo
PQ Expression, Aggregate and PAO Formation

7 mo PQ19

7 mo PQ83

(toxic amyloid)
(nontoxic control)
A proteotoxic, PAO is sufficient to cause HF
Environmental Enrichment Reduces Aβ Levels and Amyloid Deposition in Transgenic Mice

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Experimental protocol

- Trained group: 6, 1 month old male CryAB<sup>WT</sup> or CryAB<sup>R120G</sup> were placed in cages with running wheels.
- Control group- 6 CryAB<sup>WT</sup> and CryAB<sup>R120G</sup> littermates were kept in regular cages.
PAO levels

TG

TG_Tr

% of total area

TG

TG_TR
Exercise upregulates autophagy

and autophagy is compromised in the disease model
Attempt to PRECISELY up-regulate autophagy by cardiomyocyte-specific expression of Atg7
Atg7 expression reduces CryAB$^{R120G}$ aggregate content.
Atg7 siRNA knockdown: >90%

CryAB$^{WT}$  CryAB$^{R120G}$

scrambled siRNA

Atg7 siRNA
Autophagy: ↑Atg7 results in **decreased** levels of pre-amyloid oligomer

CryAB<sup>R120G</sup>  
CryAB<sup>R120G</sup> + Atg7

**decreased cell toxicity**
Will Atg7 Overexpressing Mice Induce Autophagy?

αMinAtg7 x tTA

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151x55 Atg7
132x55 Atg7

GAP

On
Off
Will Atg7 Overexpression Affect Autophagy Gene Expression?
Kaplan-Meier

Survival (days)

% Survival

R120G

TG, but ATG7 is OFF
What about exercise?

**Autophagic vacuole formation**

**Genes for Protein transport**

**Protease activity and protein targeting to vacuole**

**Autophagy in response to other intracellular signal**

**Co-regulators of autophagy and apoptosis**

**Protein ubiquitination**

**Relative expression**

- * CryABxAtg7xTA
- Ex-CryABxAtg7xTA
Kaplan-Meier

Survival Rate (%)

(Age days)

Ctrl-CryAB^{R120G} xTA
Ex-CryAB^{R120G} xTA
Ctrl-CryAB^{R120G} xAtd7xtTA
Ex-CryAB^{R120G} xAtd7xtTA

exercised
So, what else is happening during these processes?

PTMs- post-translational modifications.

Through a variety of exptl directions, we suspected that SUMOylation might be playing a role in increased aggregation in the CryAB model.
Cell Death
SUMOylation

Aggregate reduction and protein degradation

UBC9

Unfolded protein response

Cell survival and protection to oxidative stress
Summary

• Protein conformation-based pathologies play an important role in multiple cardiac and muscle skeletal diseases

• Pre-amyloid oligomers are toxic in low concentrations

• Autophagy plays an important role in protein aggregate clearance in cardiomyocytes

• Up-regulation of autophagy may lead to short or even medium term improvements in protein conformation-based cardiac disease

• Other PTM pathways may also be explored in terms of decreasing proteotoxic loads in the stressed cardiomyocyte