The Role of TRAF3IP2 in the Progression of Alcoholic Cardiomyopathy

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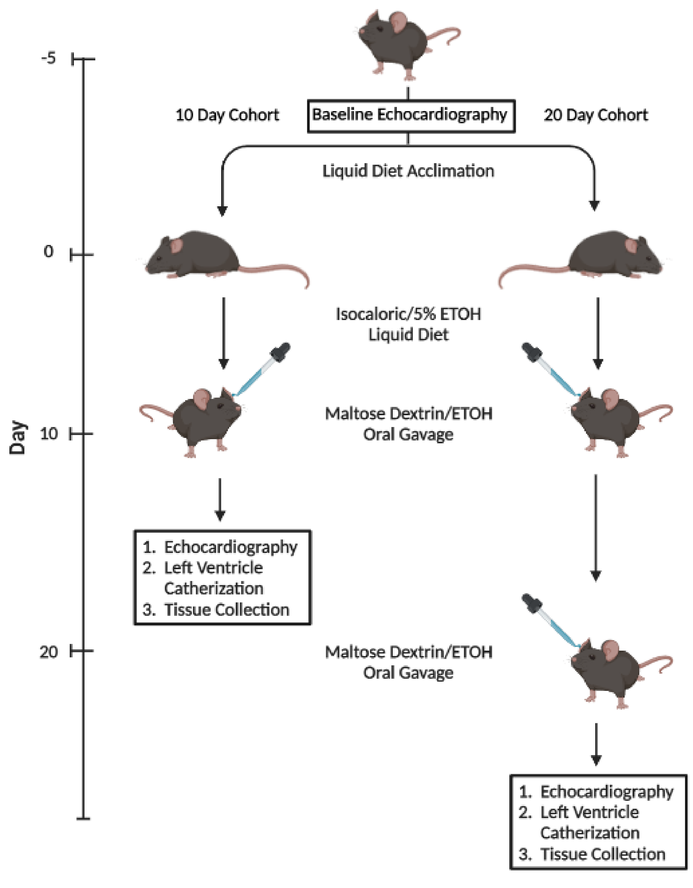
Introduction

Alcoholic Cardiomyopathy (ACM) manifests in humans after excessive alcohol consumption and is characterized by ventricular dilation and cardiac function impairment. Previous studies have identified deterioration of mitochondrial homeostasis, increased oxidative stress, and inflammation as mechanisms of ACM development.[1] However, little is known of the molecular mechanism of ACM. Here, we focus on the role of **TRAF3IP2**, a proinflammatory cytoplasmic adapter protein, in the pathogenesis of ACM. Previous work suggests TRAF3IP2 is a master regulator of inflammation; thus, being a potential therapeutic target.

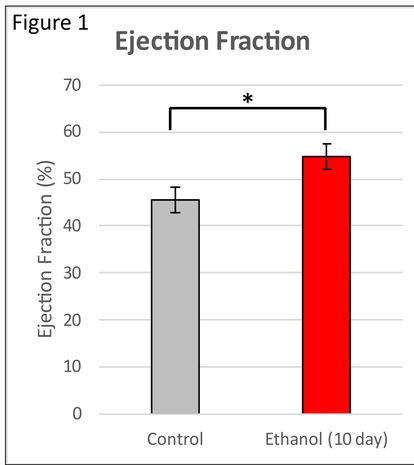
Chronic-Binge ETOH Model

In this study, we used a mouse model of chronic plus binge alcohol feeding described by the NIAAA[2]. After 5 days of acclimation to the liquid diet, mice are fed *ad libitum* 5% ethanol (EtOH) liquid diet (Lieber-DeCarli) or isocaloric control liquid diet for either 10 days or 20 days. At days 10 and 20, mice received an oral binge dose of EtOH (5 g/kg body wt), or isocaloric maltose dextrin solution (9 g/kg body wt), via oral gavage. A graphical timeline[3] is shown below:



Echocardiography

Figure 1



Echocardiography was performed at baseline and following binges to assess *in vivo* cardiac structure and function, including left ventricular thickness, stroke volume, ejection fraction, and fractional shortening.

Figure 1: *Ejection Fraction following the 10-day binge represented as percent of left ventricular volume ± SEM. Statistical analysis was done using Student's t-test where $p<0.05$ is considered significant.*

qPCR

Figure 2

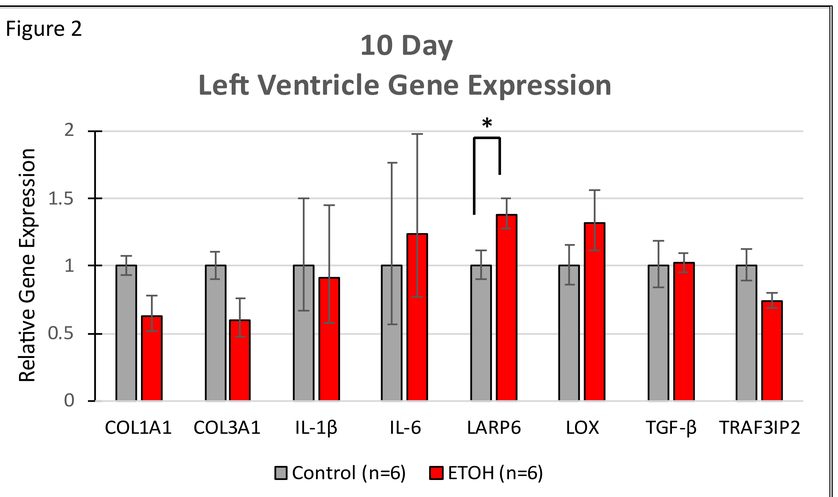


Figure 3

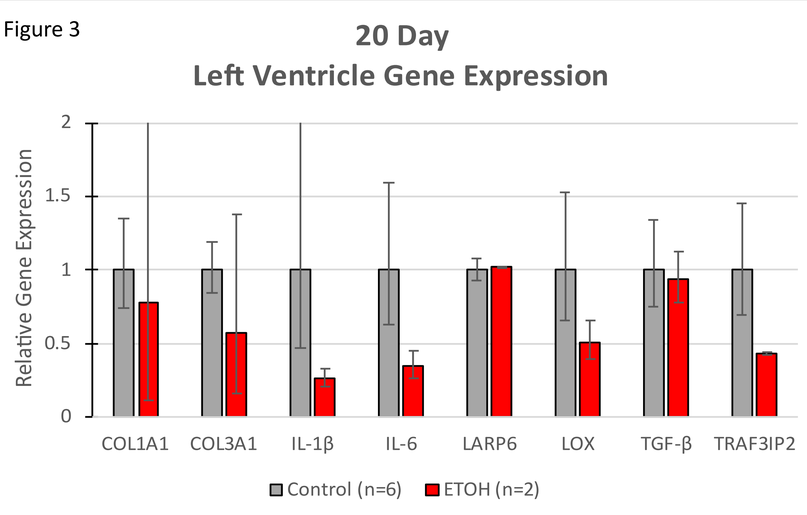


Table 1

P-values	COL1A1	COL3A1	IL-1β	IL-6	LARP6	LOX	TGF-β	TRAF3IP2
10d	0.06	0.08	0.88	0.78	**0.04***	0.24	0.91	0.05
20d	0.82	0.25	0.36	0.26	0.89	0.42	0.90	0.26

Figures 2 *and* ***3****: RNA isolated from the left ventricle was analyzed via qPCR. Gene expression was normalized using 18S rRNA as a reference gene. Student's t-test was used to assess difference in gene expression between ethanol- and control-diet cohorts. A p-value <0.05 was considered significant and results are presented as mean ± Std. P-values are shown in* ***Table 1****.*

Invasive Hemodynamics

After either 10 days or 20 days, left ventricular function was assessed via catheterization with a pressure-volume conductance catheter. End systolic pressure volume relationship (**ESPVR**) and preload recruitable stroke work (**PRSW**) are indices of contractility.

Figure 4: 20d Control

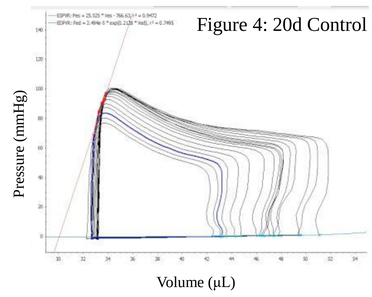


Figure 5: 20d Control

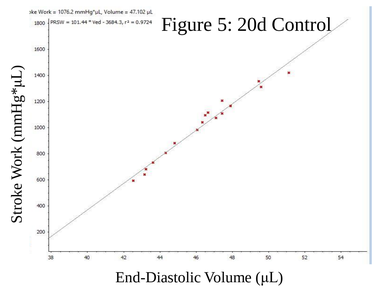


Figure 6: 20d Ethanol

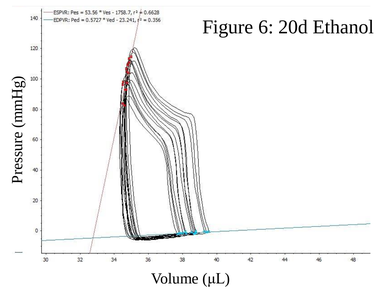


Figure 7: 20d Ethanol

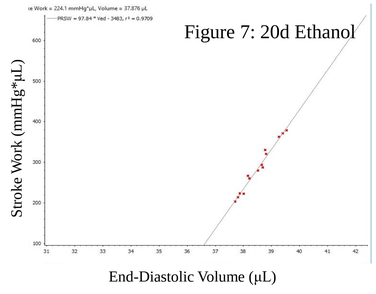


Figure 4: *PV Loop with calculated ESPVR, 20d Control Mouse.* ***Figure 5:*** *Stroke work vs End-diastolic volume with calculated PRSW, 20d Control Mouse.* ***Figure 6:*** *PV Loop with calculated ESPVR, 20d ETOH mouse.* ***Figure 7:*** *Stroke work vs End-diastolic volume with calculated PRSW, 20d ETOH mouse*

Results

- Ethanol mice at 10 days had an increased Ejection Fraction.
- LARP6 was increased following 10 days of ethanol exposure and binge.
- There were no significant differences in qPCR and echocardiography measurements between control and ethanol mice at 20 days.

Discussion

Results from this study showed little differences in gross and molecular cardiac structure and function. Further studies are needed to elucidate the role of TRAF3IP2 in the development of ACM.

References

1. Matyas et al. "Chronic plus Binge Ethanol Feeding Induces Myocardial Oxidative Stress, Mitochondrial and Cardiovascular Dysfunction, and Steatosis." *American Journal of Physiology-Heart and Circulatory Physiology* 310, no. 11 (June 2016): H1658–70.

2. Bertola, et al. "Mouse Model of Chronic and Binge Ethanol Feeding (the NIAAA Model)." *Nature Protocols* 8, no. 3 (March 2013): 627–37.

3. Created with Biorender.

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