CONTRIBUTION OF THE AMINO ACID TRANSPORTER *SLC7A5* TO PATHOLOGICAL VENTRICULAR HYPERTROPHY AND HEART FAILURE

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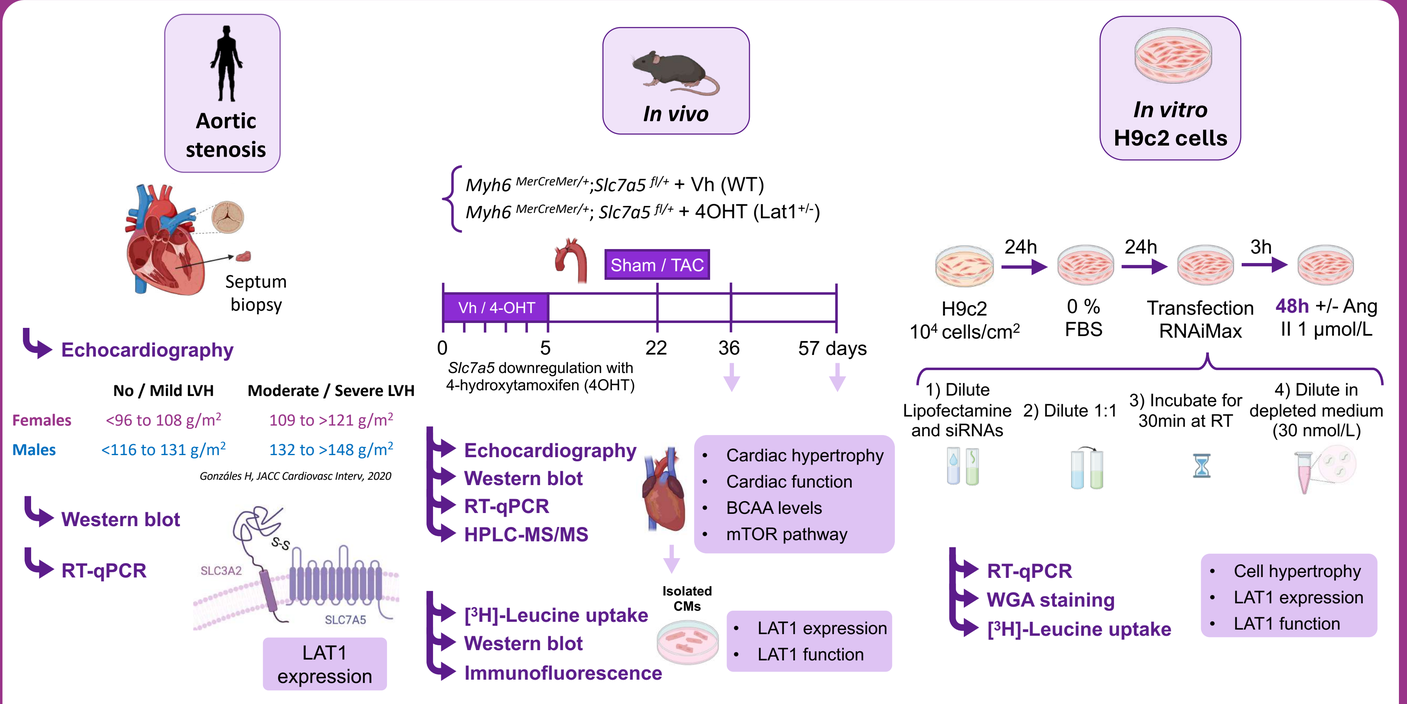
INTRODUCTION

Pathological ventricular remodelling and heart failure (HF) are associated with elevated circulating and myocardial branched-chain amino acid (BCAA) levels. Importantly, intracellular BCAAs have been shown to activate the pro-hypertrophic mTORC1 pathway, thereby contributing to the development of adverse cardiac hypertrophy. However, the mechanisms underlying myocardial BCAA accumulation remain poorly understood, particularly the potential contribution of dysregulated myocardial BCAA transport.

OBJECTIVE

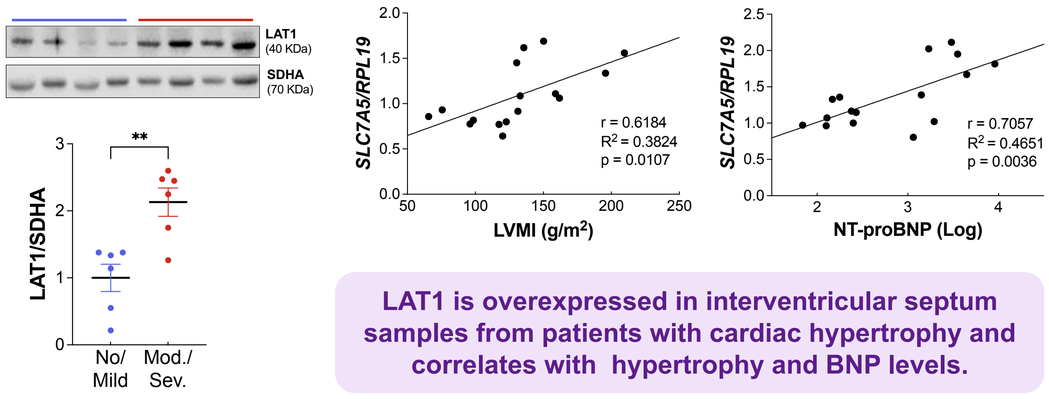
To define the causal contribution of BCAA transport via *Slc7a5* (LAT1) in cardiomyocytes to the development of pathological ventricular hypertrophy and HF induced by hemodynamic stress, and to evaluate its potential as a therapeutic target.

METHODS



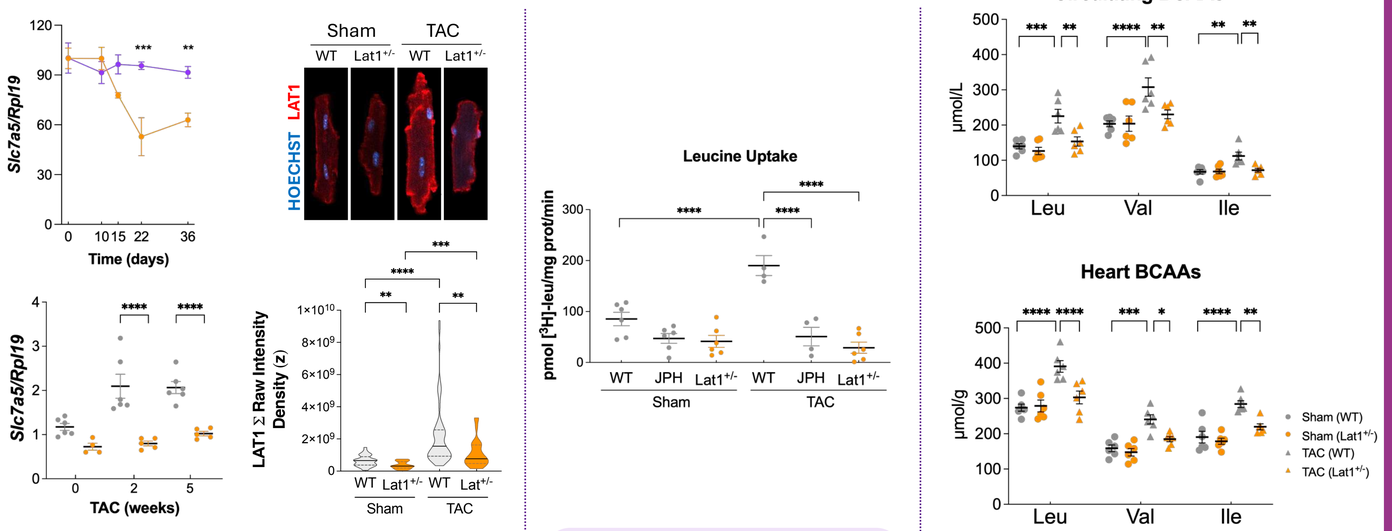
RESULTS

1. LAT1 overexpression in patients with aortic stenosis



LAT1 is overexpressed in interventricular septum samples from patients with cardiac hypertrophy and correlates with hypertrophy and BNP levels.

2. LAT1 modulates BCAA levels during pressure overload

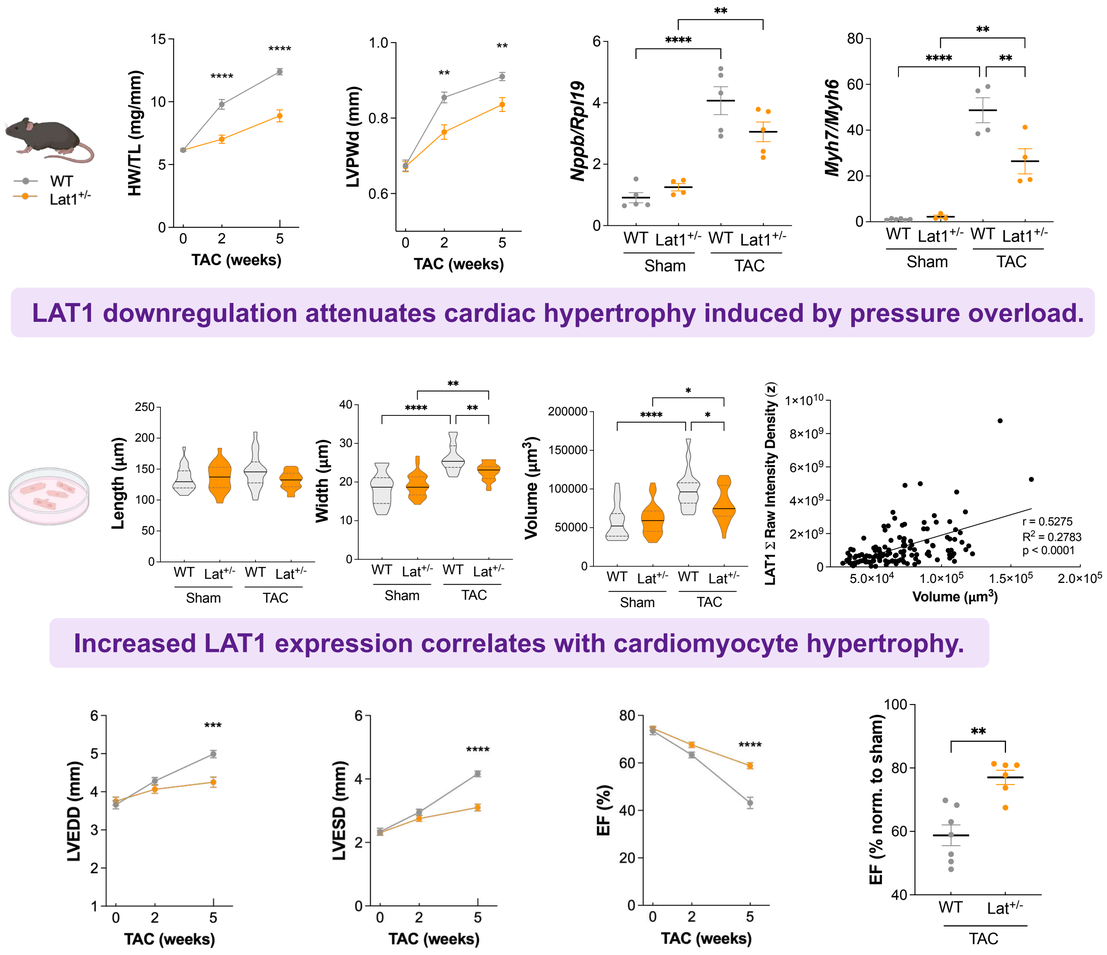


Heterozygous deletion prevents pressure overload-induced LAT1 overexpression.

LAT1 is the main driver of enhanced leucine uptake during cardiac hypertrophy development.

LAT1 downregulation reduces BCAA accumulation in the myocardium and circulation.

3. LAT1 modulates cardiac hypertrophy and function

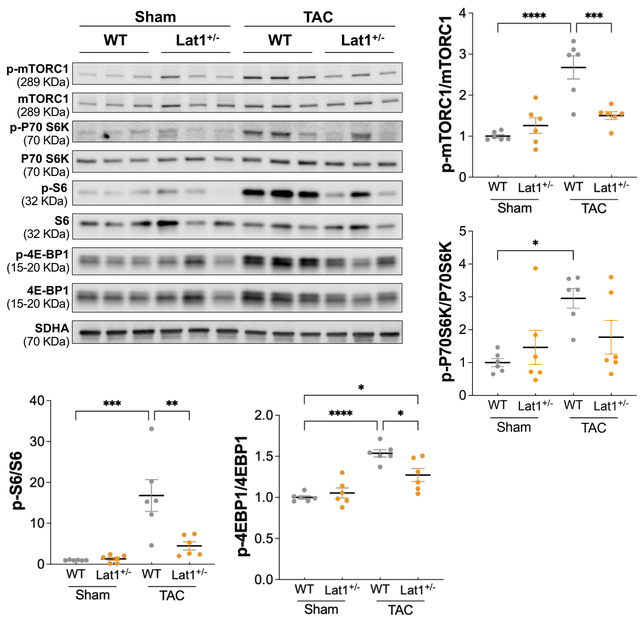


LAT1 downregulation attenuates cardiac hypertrophy induced by pressure overload.

Increased LAT1 expression correlates with cardiomyocyte hypertrophy.

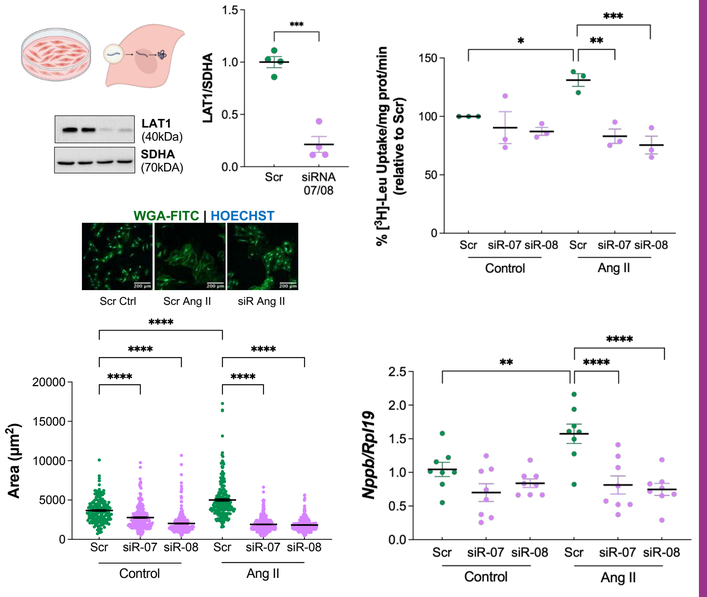
After 5 weeks of TAC surgery, ejection fraction was reduced by 41% in WT mice and by only 23% in Lat1+/- mice relative to sham controls.

4. LAT1 regulates mTOR pathway

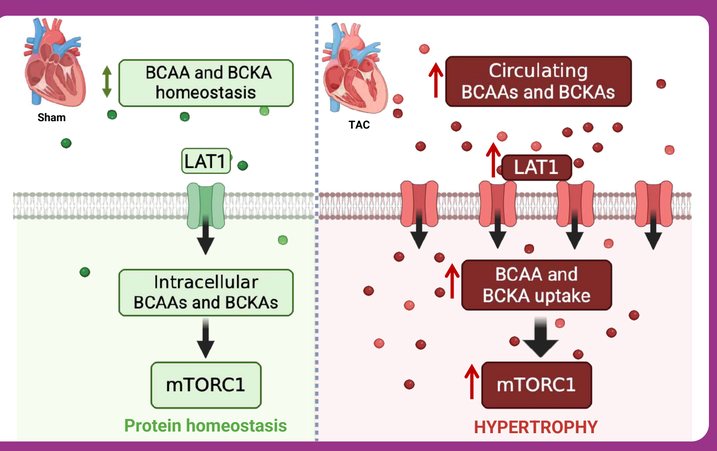


Pressure overload-induced activation of the mTOR pathway is attenuated by partial LAT1 downregulation specifically in cardiomyocytes.

5. LAT1 knockdown in Ang II-stimulated H9c2 cardiomyoblasts



LAT1 knockdown inhibits leucine uptake and hypertrophic growth in Ang II-stimulated H9c2 cells.



CONCLUSIONS

LAT1 is upregulated in cardiomyocytes in response to hemodynamic stress and plays a central role in the development of hypertrophy and HF through increased BCAA uptake and mTOR activation. Our results suggest that targeting BCAA transport may offer a novel therapeutic approach to attenuate the progression of adverse cardiac remodelling and HF.

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