Conclusions We demonstrate for the first time, that AT-derived ceramides are causally related with dysregulated myocardial redox signalling and adverse cardiovascular disease outcomes in patients with advanced atherosclerosis. As such, GlcC16 may be an important therapeutic target for the prevention and treatment of cardiovascular complications in obesity and diabetes.

Introduction Autophagy and apoptosis are both essential for cardiomyocyte homeostasis and have been implicated in cardiac remodelling following myocardial infarction (MI). A thorough understanding of these processes is crucial for the development of novel therapeutic strategies that aim to promote cardiomyocyte survival and diminish myocardial injury post-MI. Microtubule-associated protein 1S (MAP1S) was recently identified as an interactor partner of a crucial autophagy marker, LC3. However, the role of MAP1S in the heart is poorly understood. Therefore, we aimed to investigate the role of MAP1S in regulating cardiomyocyte autophagy and apoptosis.

Methods and Results To overexpress MAP1S, primary neonatal rat cardiomyocytes (NRCM) were transfected with adenovirus construct carrying MAP1S coding sequence. GFP-LC3 expressing adenovirus was used to estimate autophagic flux. Following co-treatment with rapamycin (5 μM) and chloroquine (3 μM), MAP1S-overexpressing NRCM exhibited higher autophagy activity. Similarly, immunoblot analysis of endogenous LC3-II showed a trend towards higher autophagy activity in NRCM overexpressing MAP1S compared to controls (LC3-II turnover assay). Interestingly, overexpression of MAP1S significantly reduced apoptosis in response to oxidative stress (100 μM H2O2 treatment) as determined by TUNEL assay. Consistently, siRNA-mediated gene silencing of MAP1S in NRCM increased apoptosis level following H2O2-induced oxidative stress. We next analysed whether ablation of MAP1S in mice affects cardiac phenotype following MI. We subjected MAP1S global knockout (KO) mice to coronary artery ligation and found significantly higher mortality in MAP1S-KO mice (60%) compared to wild-type counterparts (30%) 4 week post-MI. TUNEL assay demonstrated that cardiomyocyte apoptosis was elevated in MAP1S-KO mice at both 3 days and 4 weeks post-MI. These results triggered us to identify MAP1S interactor partners and associated pathways which could explain the involvement of MAP1S in apoptosis. In-silico analysis found 46 experimentally validated MAP1S interacting proteins expressed in the heart. Furthermore, KEGG and Reactome pathway analysis revealed that MAP1S interactor partners are primarily associated with the Hippo signalling pathway. Conclusion. Our findings suggest that MAP1S has a pivotal role in cardiomyocyte survival by regulating autophagy and apoptosis. MAP1S may be involved in apoptosis via the Hippo pathway.

Conclusions Our findings suggest that changes in mitochondrial protein lysine acetylation represent a key metabolic component of diastolic dysfunction that precedes the development of heart failure. Our work suggests that manipulation of PDHA1 acetylation levels in vivo may represent a novel target for therapeutic intervention in the treatment of diastolic dysfunction.