**METHODS**

**Human tissue sampling**

The investigation conforms to the principles outlined in the Declaration of Helsinki. The institutional ethics committee approved the study, and all patients provided written informed consent for the use of cardiac tissue samples. Human ventricular muscle tissue was obtained from freshly explanted hearts of six end-stage heart failure patients undergoing cardiac transplantation as a result of ischemic or dilated cardiomyopathy and from six donor hearts that could not be transplanted due to clinical reasons and from aortic stenosis valve operation with Morrow resection. Detailed patient characteristics are provided in the online supplement (Table S1). Healthy human hearts (no pre-existing cardiac disease and noncardiac reason of death) that initially were planned for transplantation but in the end were rejected by the surgeon served as controls. Reasons for rejection were organ mismatch, elevated serum C-reactive protein levels, local hypokinesia. Available information about heart donor individuals are given in the supplementary table S2.

**Transverse aortic constriction (TAC) in mice**

The investigation conforms to the Guide for the Care and Use of Laboratory Animals (NIH publication No. 85–23, revised 1996) and was performed in accordance with the ethical standards laid down in the [Declaration of Helsinki](http://link.springer.com/search?dc.title=Declaration+of+Helsinki&facet-content-type=ReferenceWorkEntry&sortOrder=relevance) 1964. Surgery was done using a minimally invasive approach. Briefly, 8-week-old female FVBN mice were anesthetized using intraperitoneal injections of a mixture of xylazine and ketamine. A 27 gauge needle was tied against the aorta using a 5-0 non-absorbable suture. Sham animals underwent the same procedure except banding of the transverse aorta.

**Generation of *Fto* cKO mice**

In order to create *Fto*-flox mice, the B6Dnk;B6Brd;B6N-Tyrc-Brd Ftotm1a(EUCOMM)Wtsi/WtsiCnbc strain (Wellcome Trust Sanger Institute) was crossed with C57BL/6N-Tg(CAG-Flpo)1Afst/Mmucd strain [Kranz A, et al., Genesis. 2010 Aug;48(8):512-20] to first remove the lacZ-neomycin cassette. The obtained mice were back-crossed with C57BL6/N wildtype mice to get rid of the *Flpo* allele finally resulting in mice where Exon 3 of *Fto* is flanked by loxP sites (*Fto*fl/fl).

The conditional *Fto* knock-out was created by mating male *Fto*fl/fl mice with the cardiomyocyte specific *αMHC-Cre* females (*αMHC-Cre*, Jackson no. 011038, C57BL/6N and C57BL/6J mixed background; [Agah et al. 1997]). For experiments, resulting *αMHC-Cre*+;*FTO* fl/fl mice (Cre+ fl/fl) bearing the homozygous *Fto* knock-out were used.

As wildtype control *αMHC-Cre*+ mice (Cre+ +/+) as well as *αMHC-Cre*-;*Fto* fl/fl mice (Cre- fl/fl) were used to rule out Cre- recombinase and loxP system derived effects.

**Echocardiography**

The mice were anaesthetized using 1.5% isoflurane, and echocardiography was performed using a VS-VEVO 660/230 (Visualsonics, Toronto, Canada). 2D guided M-mode images were recorded in the long-axis view at the left mid-ventricular level. The examiner was blinded towards group assignment.

**Murine LV-Isolation**

Subsequent to the Echocardiography, mice were anesthetized with Isoflurane and killed via cervical dislocation. The heart was isolated and flushed with 0.9% NaCl through the aorta, the LV was separated and snap-frozen in liquid nitrogen.

**Western blot analysis**

Up to 30 mg of snap-frozen tissue from murine or human LV was homogenized with the MICCRA D-9 (MICCRA; #090000) in ice-cold RIPA buffer (Merck; #20-188) supplemented with protease- and phosphatase inhibitors (Roche, Basel, CH, #04693159001; #04906845001). Protein concentration was determined with the Pierce BCA Protein Assay Kit (Thermo Fisher Scientific; #23225).

20µg of protein samples were first denatured and then separated using 4-20% TGX Gels (Bio-Rad; #4568096, followed by transfer onto a Nitrocellulose Membrane (Bio-Rad, Hercules, CA; **#**1620214). Membranes were incubated with anti-FTO (1:1000; NBP2-29512, Novus Biologicals, Bio-Techne, Minneapolis, MN), anti-METTL3 (1:1000; 15073-1-AP, Proteintech, Rosemont, IL), anti-METTL14 (1:1000; SC-247960, Santa Cruz Biology, Dallas, TX), anti-METTL16 (1:1000; PA5-54185, Thermo Fisher Scientific, Waltham, MA), anti-CALM1 (1:1000, LS-C331329-50, LifeSpan BioSciences, Seattle, WA), anti-Calm1 (1:1000, ab45689, Abcam, Cambridge, United Kingdom), anti-Smyd1 (1:10000, GTX119484, Genetex, Irvine, CA) and anti-GAPDH (1:30000; MAB374; Merck, Burlington, MA) [all in 1% Milk/TBST]. ECL anti-Rabbit igG (1:10000; Amersham/GE-Healthcare Life Sciences, Little Chalfont, UK), ECL anti-Mouse igG (1:10000; Amersham/GE-Healthcare Life Sciences, Little Chalfont, UK) and ECL anti-Goat igG (1:10000; Agilent, CA) were used as secondary antibodies. Antibody was detected using the SuperSignal™ West Femto Maximum Sensitivity Substrate (34095; Thermo Fisher Scientific, Waltham, MA). Bands of protein of interest were normalized to GAPDH.

**Me-RIP-seq**

Total RNA from the left ventricles was isolated with Trizol Reagent (Thermo Fisher Scientific, #15596018) following manufacture’s instruction. After DNAse treatment rRNA was removed using NEBNext rRNA Depletion Kit (NEB, #E6310, Ipswich, MA) and purified large RNA fraction (>200 bp) was fragmented to about 80 nt by RNA Fragmentation Reagent at 70°C for 12 min (#AM8740, Thermo Fisher Scientific, Waltham, MA). 8% of RNA samples was kept as inputs and the rest was subjected to immunoprecipitation in10mM Tris-HCl pH 7.4, 150mM NaCl and 0.1% (vol/vol) Igepal CA-630 buffer supplemented with 200 U RNasin Plus RNase Inhibitor (#2611, Promega) and 2mM RVC (#R3380, Sigma-Aldrich). 5 µg of anti-m6A polyclonal antibody (Synaptic Systems, #202003) conjugated to Dynabeads Protein G (Thermo Fisher Scientific, #10003D) was added to the RNA and was incubated at 4°C ON. The beads were washed with 1x IP buffer three times, and m6A RNA was eluted twice with 6.7mM N6-methyladenosine (Sigma-Aldrich, M2780) in 1x IP buffer. The eluted RNA fragments were purified with ZymoResearch RNA Clean and Concentrator-5 (Zymo Research, #R1015), cDNA libraries were prepared from input and immunoprecipitated samples using TruSeq Stranded Total RNA Library Prep Kit (#20020596, Illumina) and sequenced on Illumina HiSeq 2000.

**Analysis of NGS data**

For RNA methylation analysis first adapters were trimmed from the original reads and low quality reads were removed. The remaining reads were mapped to the mouse genome (mm10) using STAR tools. Mapped reads were sorted and indexed with SAMtools and generated bam files of input and immunoprecipitated samples were generated. Peaks showing significant enrichment in the immunoprecipitated samples vs. corresponding input samples for all submitted replicates were detected using MeTPeak package [12]. Only those with false discovery rate (FDR) values equal to or less than 0.05 were considered as real m6A peaks. All peaks were assigned based on their position in mRNA, in particular 5’untranslated region (5’UTR), coding sequence (CDS) and 3’untranslated region (3’UTR). Few peaks mapped to non-coding RNAs were identified as well.

For differential methylation analysis we used in-house developed pipeline. In brief, peaks overlapping or unique for treated and control samples were detected using BEDTools and fold changes with joined p values were calculated for the hypo- and hypermethylated peaks. mRNAs showing significant (p-value < 0.05) and at least 2 fold change in the methylation levels for all peaks detected for the given transcript are considered in this study.

For the comparison of transcriptome of control and affected heart tissue, differential expression analysis was conducted of input samples using DESeq2. Genes with transcripts levels showing 2 fold and/more changes in their transcripts levels with padj values equal to or less than 0.05 were considered as differentially expressed.

**qRT-PCR verification of differentially methylated transcripts**

RNA was reverse transcribed into cDNA by using Transcriptor First Strand cDNA Synthesis Kit (Roche, Mannheim, Germany) followed by quantitative Real-Time PCR analysis on LightCycler 480 System (Roche, Mannheim, Germany). LightCycler 480 parobes master mix was used in reaction with FAM-labeled probes from the Universal Probe Library: #48 for *CALM1* (forward primer 5’- taccacgaacccctcagc -3’ and reverse primer 5’- gaccaaatttacattcgttgttca-3’), #89 for *Calm1* (forward primer 5’- gctgcaggatatgatcaacg-3’ and reverse primer 5’- agaactctgggaagtcaatggt-3’), #40 for *Gata6* (forward primer 5’- ggtctctacagcaagatgaatgg-3’ and reverse primer 5’- tggcacaggacagtccaa-3’), #96 *Rnd3* (forward primer 5’- cggacagatgtcagcacatt-3’ and reverse primer 5’- tctgcttggccatatttgc-3’), #17 for *Smyd1* (forward primer 5’- catgtttcacacgcagatga-3’ and reverse primer 5’- aggtgcaggaagtctatgtagga-3’). Ratios between immunoprecipitated and input RNAs for normal mouse and human heart tissues were set to one.

**Analysis of polysome-associated RNAs**

Polysomes were prepared from the heart tissue of five TAC and five control animals as described [13]. Briefly, tissue samples were lysed in a buffer containing 50 mM Tris-HCl pH 7.4, 10 mM MgCl2, 100 mM NaCl, 1% Triton-X-100, 1 mM DTT, RNase inhibitors and 100 μg/ml cycloheximide using a MICCRA D-1 homogenizer. Cell debris were removed by centrifugation at 20,000 x g for 10 min at 4 °C. The soluble whole cell extracts were separated on 10-50% sucrose density gradients (prepared in 50 mM Tris-HCl pH 7.4, 10 mM MgCl2, 100 mM NaCl, 1 mM DTT and 100 μg/ml cycloheximide) in an SW-40Ti rotor by centrifugation for 3 h at 35,000 rpm. Fractions containing polysomes (determined by monitoring the absorbance of each fraction at 260 nm) were pooled and RNAs were extracted using phenol:chloroform:isoamylalcohol (25:24:1), ethanol precipitated and resuspended in water. The cDNA libraries were constructed using TruSeq Stranded Total RNA Library Prep Kit (#20020596, Illumina) and sequenced on Illumina HiSeq 2000. DESeq2 package was used to detect enriched and depleted transcripts in polysomal bound RNA vs. input samples and those with at least 2 fold change and p*adj* values equal to or less than 0.05 were reported as transcripts translated differentially.

**Pathway analysis**

We used ClueGO plug-in (version 2.3.2) in the open source software platform Cytoscape for creation and visualization of functionally grouped networks of GO terms and pathways. Parameters were following: Network Specificity – medium, Bonferroni corrected p-value < 0.01. GO categories form “Biological Process” were extracted and plotted with their p-values.

**Data availability**

The raw sequencing and processed data reported in this study have been deposited in NCBI’s Gene Expression Omnibus and are accessible through GEO seies accession number GSE131296 (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE131296>).