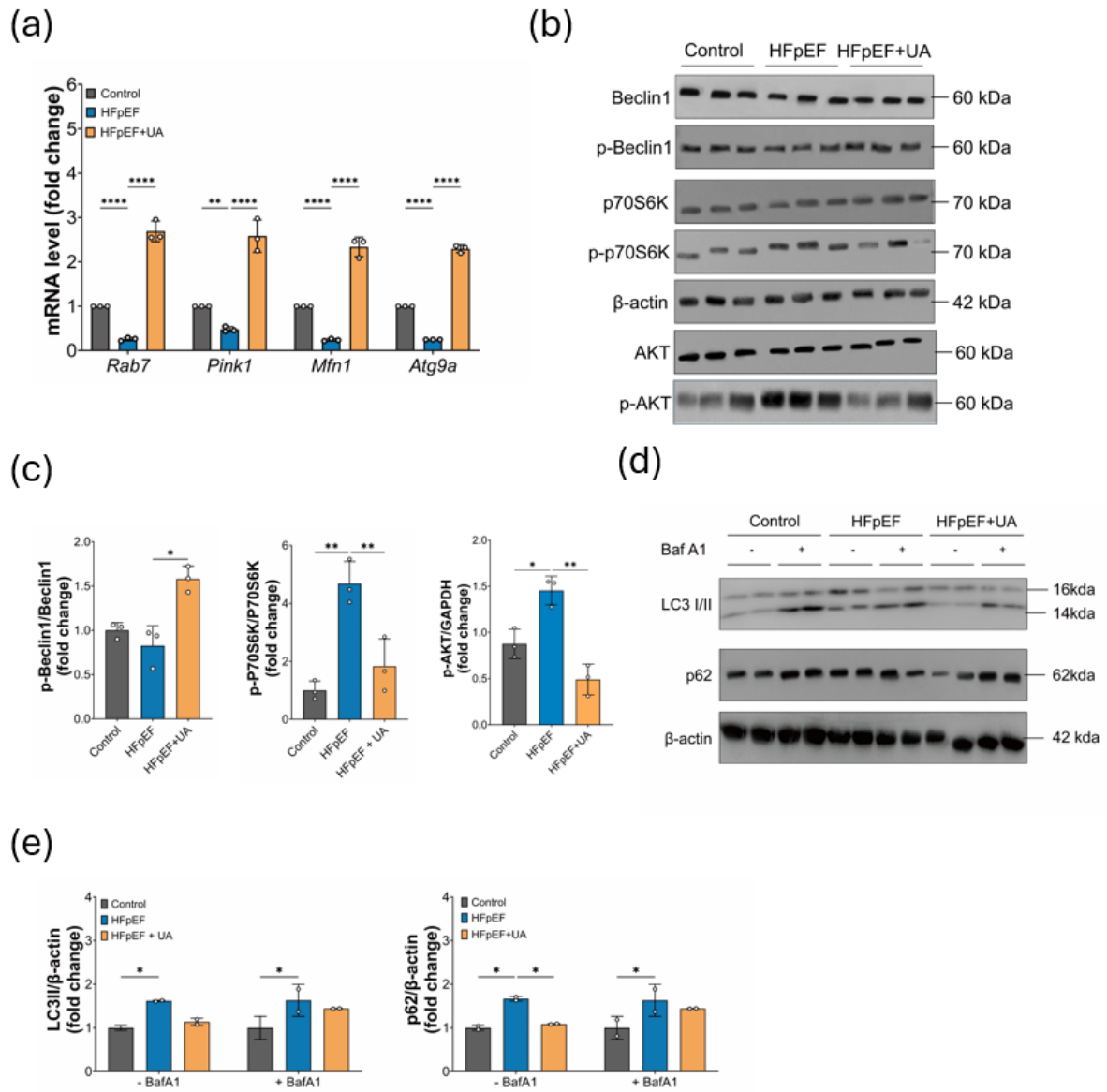


Supplementary Table 1. Primer sequences used for RT-PCR

Gene	Species	Direction	Sequence (5' → 3')
<i>Mouse primers</i>			
<i>Tgf beta-1</i>	Mouse	Forward	CCTGTCCAAACTAAGGC
	Mouse	Reverse	GGTTTTCTCATAGATGGCG
<i>Col1a1</i>	Mouse	Forward	GAGCGGAGAGTACTGGATCG
	Mouse	Reverse	GCTTCTTTTCCTTGGGGTTC
<i>Ctgf</i>	Mouse	Forward	CAAAGCAGCTGCAAATACCA
	Mouse	Reverse	GGCCAAATGTGTCTTCCAGT
<i>Myh7</i>	Mouse	Forward	CACCGCTCACCTTCACCCG
	Mouse	Reverse	TTCCACCTAAAGGGCTGTTG
<i>Bnp</i>	Mouse	Forward	TCCATCAGAGGGGTCACAC
	Mouse	Reverse	GCCTTGTAAGGGGTGATTA
<i>Scd1</i>	Mouse	Forward	CCTGTACGCTGGTGTGAAT
	Mouse	Reverse	CACGTTGGGTGCGATGAAGAA
<i>Rab7</i>	Mouse	Forward	ACTGCCCCCAACACTTTCAA
	Mouse	Reverse	CTTGGCACTGGTCTCGAAGT
<i>Pink1</i>	Mouse	Forward	CACACTGTTCTCGTTATGAAGA
	Mouse	Reverse	CTTGAGATCCCGATGGGCAAT
<i>Mfn1</i>	Mouse	Forward	ATCACTGCAATCTTCGGCCA
	Mouse	Reverse	AGCAGTTGGTTGTGTGACCA
<i>Atg9a</i>	Mouse	Forward	CGCTGTGGACAAAGTGATGA
	Mouse	Reverse	GCTGGTAGATGGTGTGAGG
<i>Human primers</i>			

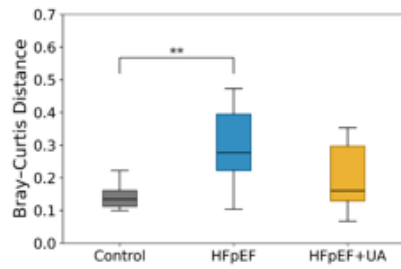
Gene	Species	Direction	Sequence (5' → 3')
<i>IL6</i>	Human	Forward	AGTAGTGAGGAACAAGCCAGAG
	Human	Reverse	TACATTTGCCGAAGAGCC
<i>IL8</i>	Human	Forward	GAGAGTGATTGAGAGTGGACCAC
	Human	Reverse	CACAACCCTCTGCACCCAGTTT
<i>IL1B</i>	Human	Forward	CCACAGACCTTCCAGGAGAATG
	Human	Reverse	GTGCAGTTCAGTGATCGTACAGG
<i>TGFBI</i>	Human	Forward	TCGACATGGAGCTGGTGAAG
	Human	Reverse	GGTTTCCACCATTAGCACGC
<i>COL1A1</i>	Human	Forward	GAGGGCCAAGACGAAGACATC
	Human	Reverse	CAGATCACGTCATCGCACAAAC
<i>CTGF</i>	Human	Forward	CAAGGGCCTCTTCTGTGACT
	Human	Reverse	CCGTCGGTACATACTCCACA
<i>BNP</i>	Human	Forward	TCAGCCTCGGACTTGGAAC
	Human	Reverse	CTTCCAGACACCTGTGGGAC
<i>ANP</i>	Human	Forward	GAACCAGAGGGGAGAGACAGAG
	Human	Reverse	CCCTCAGCTTGCTTTTATAGGAG
<i>MYH6</i>	Human	Forward	GGAAGACAAGGTCAACAGCCTG
	Human	Reverse	TCCAGTTTCCGCTTTGCTCGCT
<i>MYH7</i>	Human	Forward	AGACTGTCGTGGGCTTGTATCAG
	Human	Reverse	GCCTTTGCCCTTCTCAATAGG



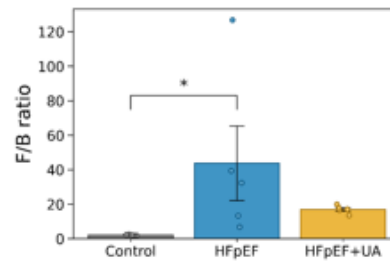
Supplementary Figure 1. (a) Quantitative PCR analysis of autophagy- and mitophagy-related genes in cardiac tissue from Control, HFpEF, and HFpEF+UA mice. (b) Immunoblot analysis of phospho-Beclin-1/Beclin-1, phospho-p70S6K/p70S6K, phospho-AKT/AKT and in heart lysates; β -actin was used as a loading control. (c) Densitometric quantification of phospho-mTOR/mTOR, phospho-AKT/AKT, and phospho-AMPK α /AMPK α ratios. (d) Immunoblot analysis of autophagy initiation-related proteins, including Beclin1, ULK1, p70S6K; β -actin was used as a loading control. (e) Densitometric quantification of phospho-Beclin1/Beclin1, phospho-ULK1/ULK1, and phospho-

p70S6K/p70S6K ratios. Data are presented as mean $\pm$ SEM. Statistical significance was assessed as described in the Methods. *P<0.05, **P<0.01, ***P<0.001, ****P<0.0001.

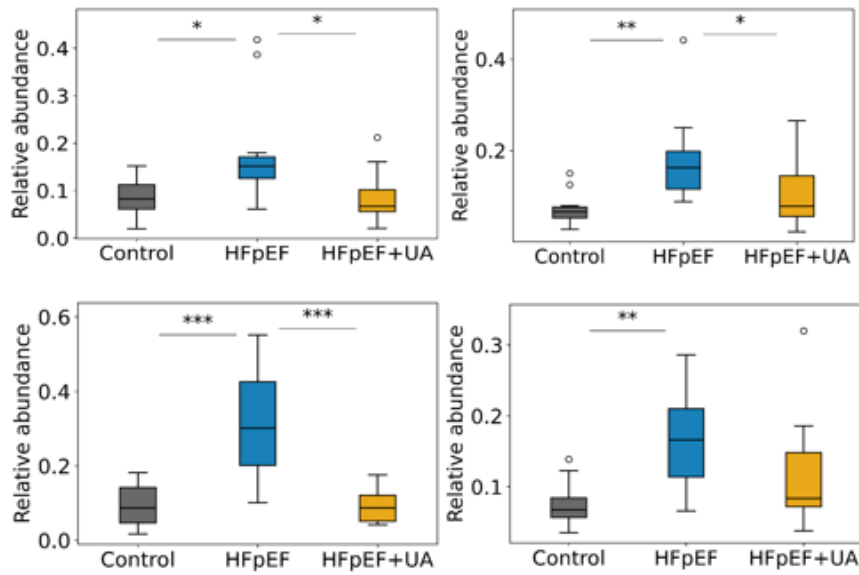
(a)



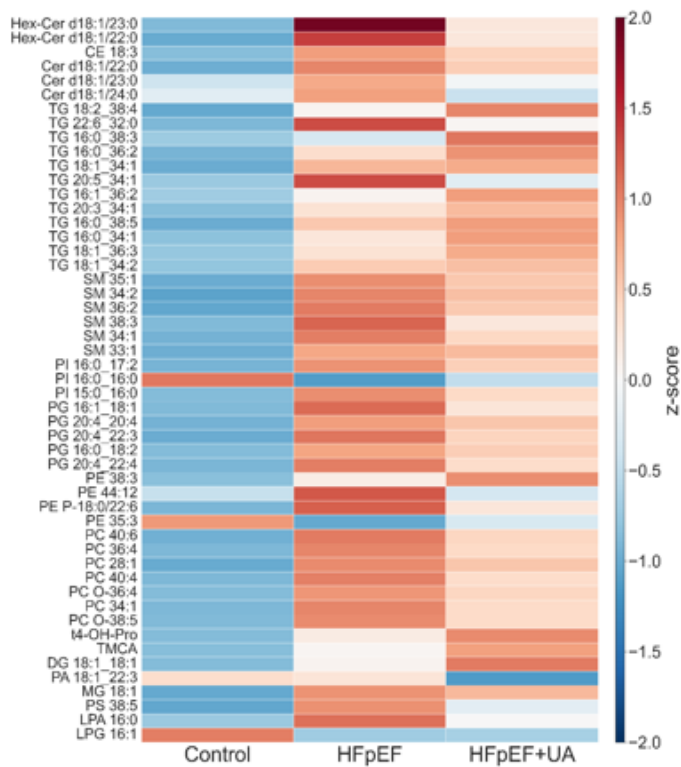
(b)



(c)

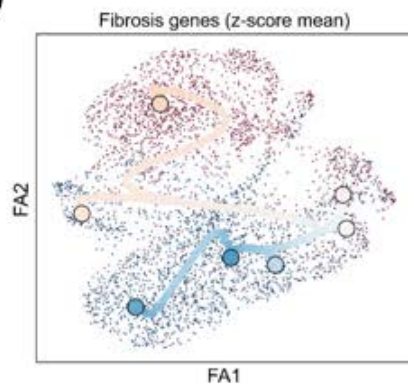


(d)

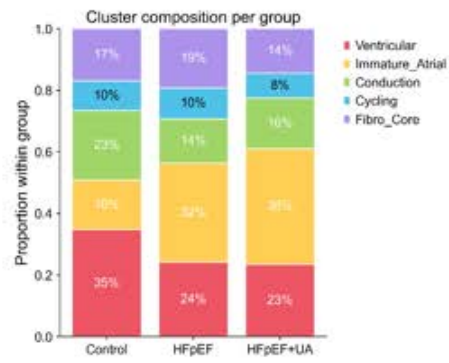


Supplementary Figure 2. Gut microbiome composition and lipidomic features associated with HFpEF and UA treatment. **(a)** Bray–Curtis dissimilarity analysis comparing fecal microbial community composition among Control, HFpEF, and HFpEF+UA groups. **(b)** Firmicutes/Bacteroidetes (F/B) ratio calculated from metagenomic profiles. **(c)** Relative abundance of selected ceramide-producing bacterial genera across experimental groups, shown from left to right as Bacteroides, Parabacteroides, Phocaeicola, and Alistipes. **(d)** Z-score heatmap of selected lipidomic species across Control, HFpEF, and HFpEF+UA groups. Data are presented as mean $\pm$ SEM. Statistical significance as assessed as described in the Methods. *P<0.05, **P<0.01, ***P<0.001.

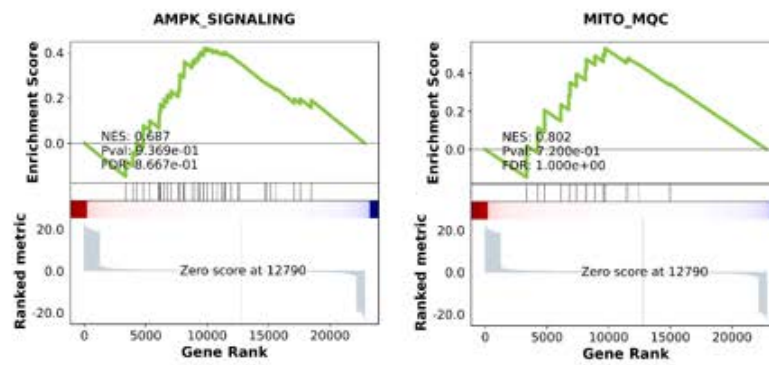
(a)



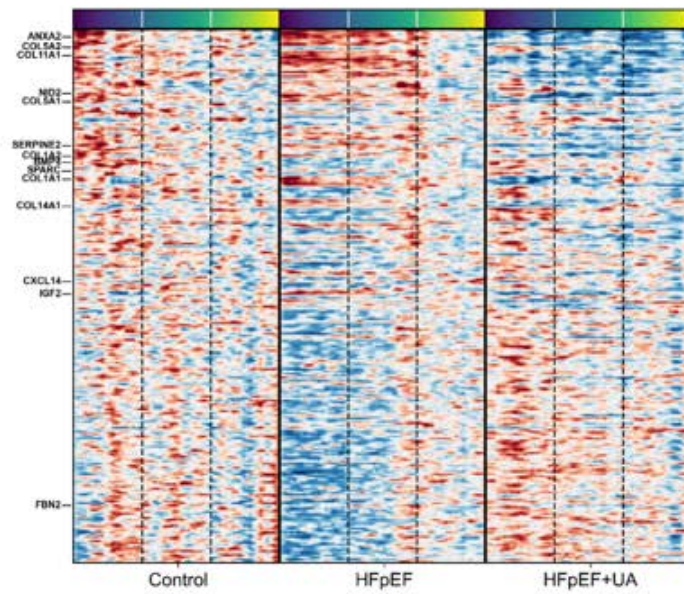
(b)



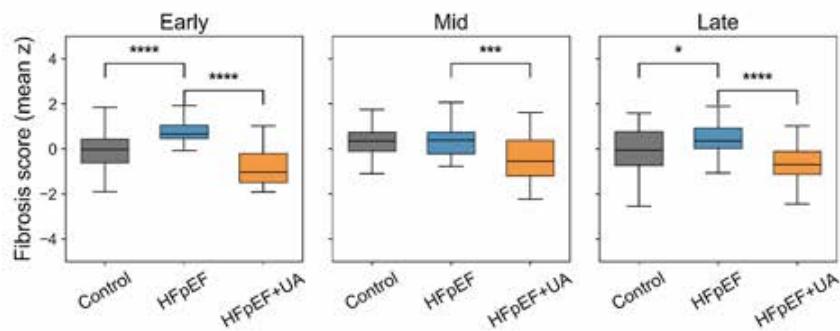
(c)



(d)



(e)



Supplementary Figure 3. Fibrosis-associated transcriptional programs and cardiomyocyte state dynamics. **(a)** ForceAtlas2 (FA1–FA2) embedding of cardiomyocyte nuclei visualizing the mean Z-score expression of a fibrosis-associated gene panel along inferred transcriptional trajectories. **(b)** Relative composition of major cardiomyocyte transcriptional modules across Control, HFpEF, and HFpEF+UA groups. **(c)** Directional GSEA changes in AMPK signaling and mitochondrial quality control with UA treatment **(d)** Heatmap of significantly altered fibrosis-related genes within fibroblast-enriched transcriptional states, showing per-cell scaled expression across Control, HFpEF, and HFpEF+UA cardiomyocytes. **(e)** Pseudotime dynamics of the fibrosis gene module, displayed as mean Z-score panel scores across Early, Mid, and Late pseudotime phases in Control, HFpEF, and HFpEF+UA cardiomyocytes.