

Appendix for:

**Homeostatic control of energy metabolism by
monocyte-derived macrophages**

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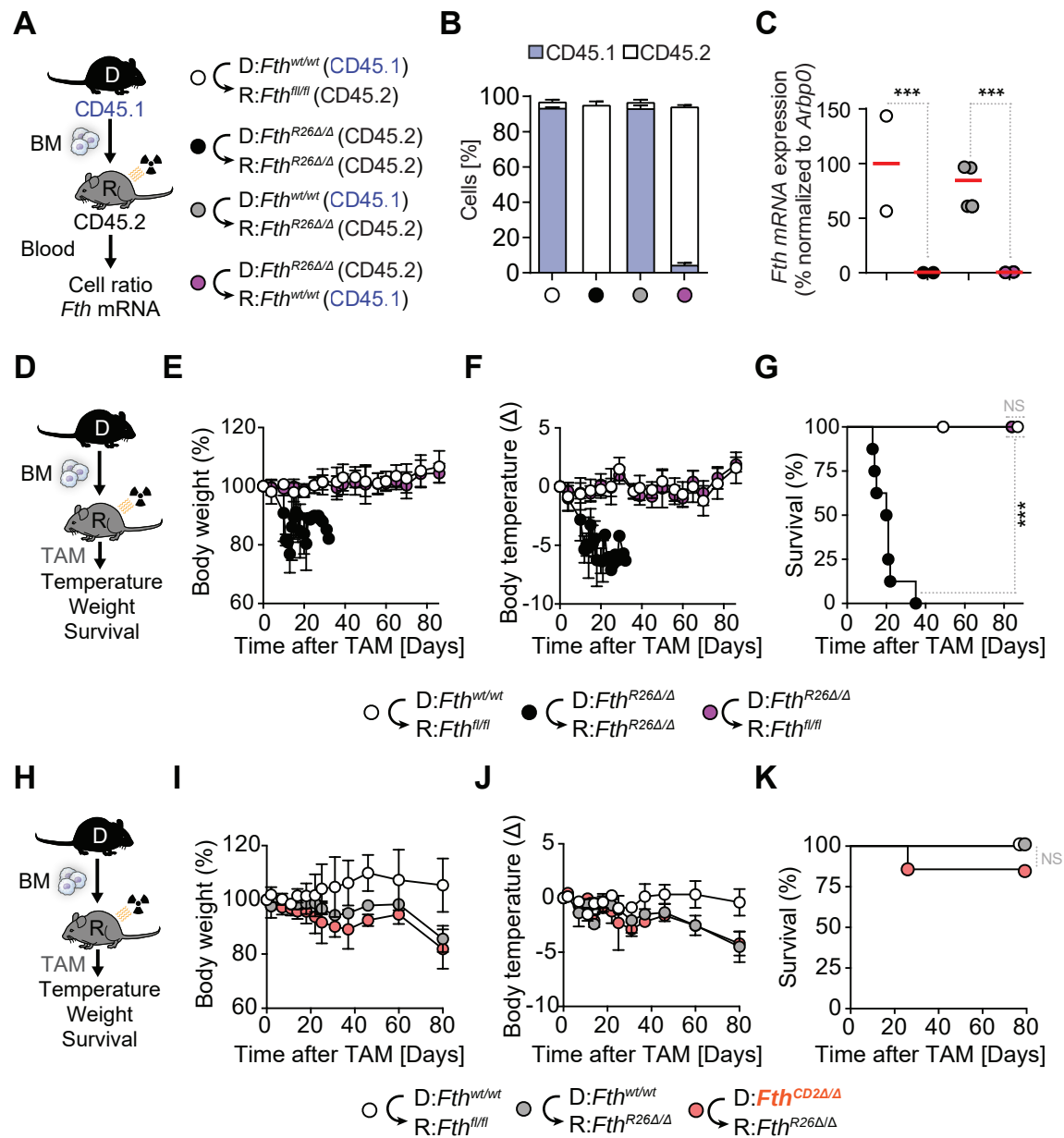
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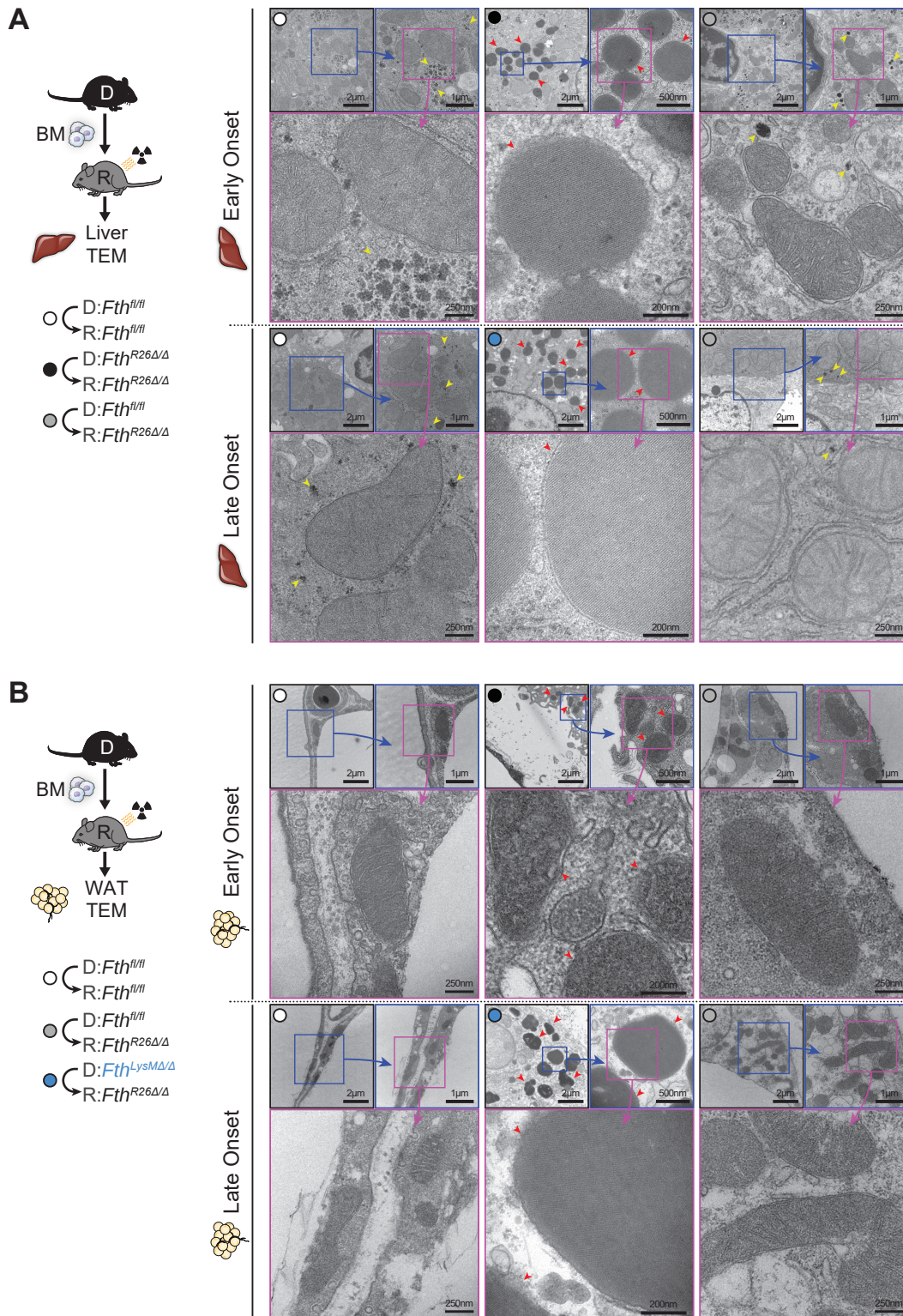
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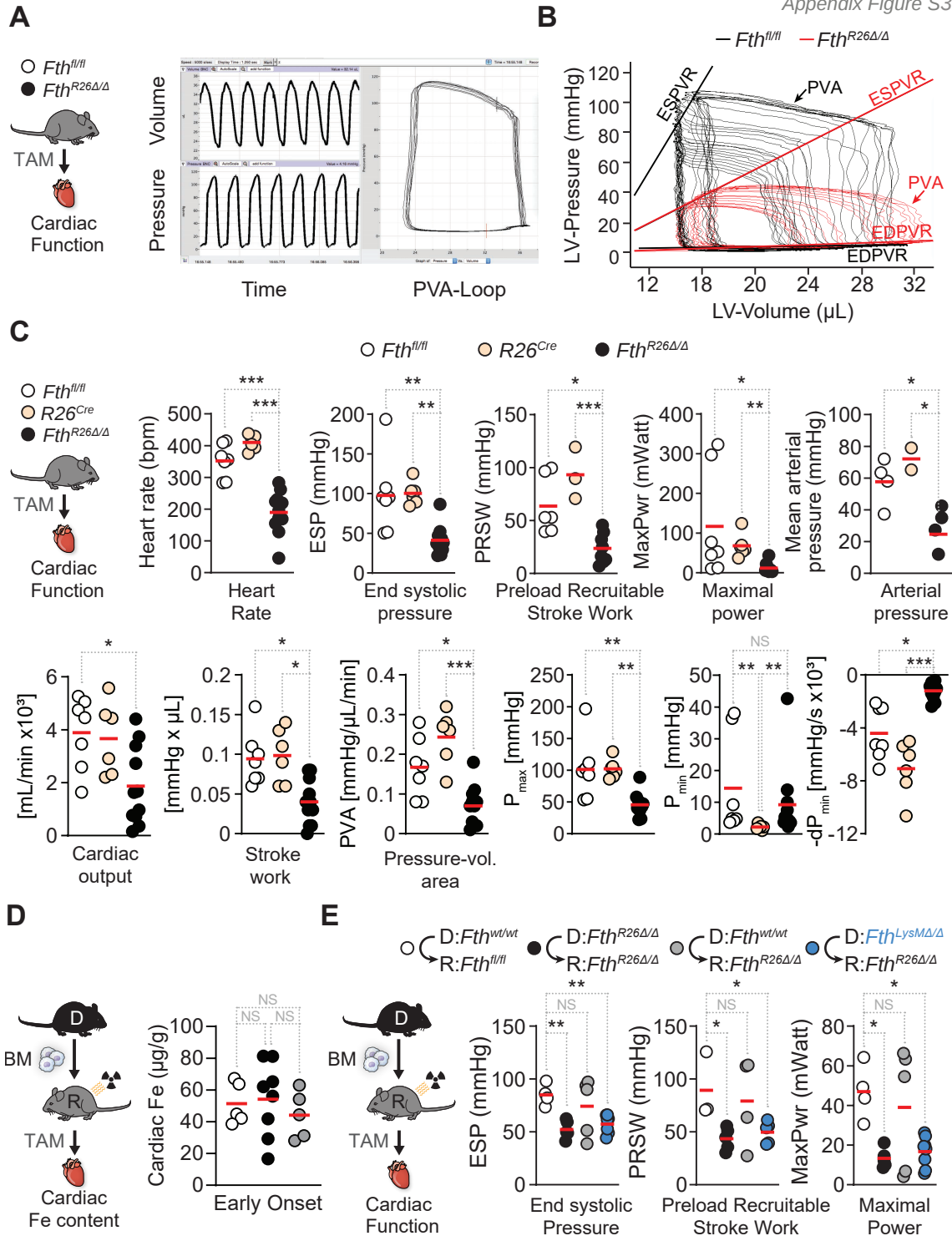
Appendix Figure S1: *Fth*-competent chimeric mice, rescue from whole-body *Fth* deletion-induced lethality independently of T-lymphocytes. (A) Schematic representation of chimeric mice and engraftment assessment. (B) Relative immune cell percentage of donor or recipient origin and (C) corresponding *Fth* gene expression in the blood of *Fth*^{wt/wt}⇒*Fth*^{wt/wt} (n=2), *Fth*^{R26Δ/Δ}⇒*Fth*^{R26Δ/Δ} (n=2), *Fth*^{wt/wt}⇒*Fth*^{R26Δ/Δ} (n=3) and *Fth*^{R26Δ/Δ}⇒*Fth*^{wt/wt} (n=2) chimeric mice, collected on day 10 post-TAM administration, as determined via flow cytometry analysis (B) and qRT-PCR (C). (D) Schematic representation of TAM-induced *Fth* deletion in chimeric mice and monitoring vital parameters. Relative body weight (E), temperature (F) and survival (G) of *Fth*^{fl/fl}⇒*Fth*^{fl/fl} (n=8), *Fth*^{R26Δ/Δ}⇒*Fth*^{R26Δ/Δ} (n=8) and *Fth*^{R26Δ/Δ}⇒*Fth*^{fl/fl} (n=8) chimeric mice following TAM administration on day 0. Data in (E, F) is represented as mean ± SD. Data in (E-G) is pooled from 3 experiments. (H) Schematic representation of TAM-induced *Fth* deletion in chimeric mice and monitoring vital parameters. Relative body weight (I), temperature (J)

and survival (**K**) of $Fth^{wt/wt} \Rightarrow Fth^{fl/fl}$ (n=3), $Fth^{wt/wt} \Rightarrow Fth^{R26\Delta/\Delta}$ (n=3) and $Fth^{CD2\Delta/\Delta} \Rightarrow Fth^{R26\Delta/\Delta}$ (n=7) chimeric mice following TAM administration on day 0. Data in (I, J) is represented as mean $\pm$ SD. Data in (I-K) is pooled from 2 experiments. One-Way ANOVA with Tukey's range test for multiple comparison correction was used for comparison between multiple groups. Survival analysis was performed using Log-rank (Mantel-Cox) test. NS: non-significant, *** $P < 0.001$.



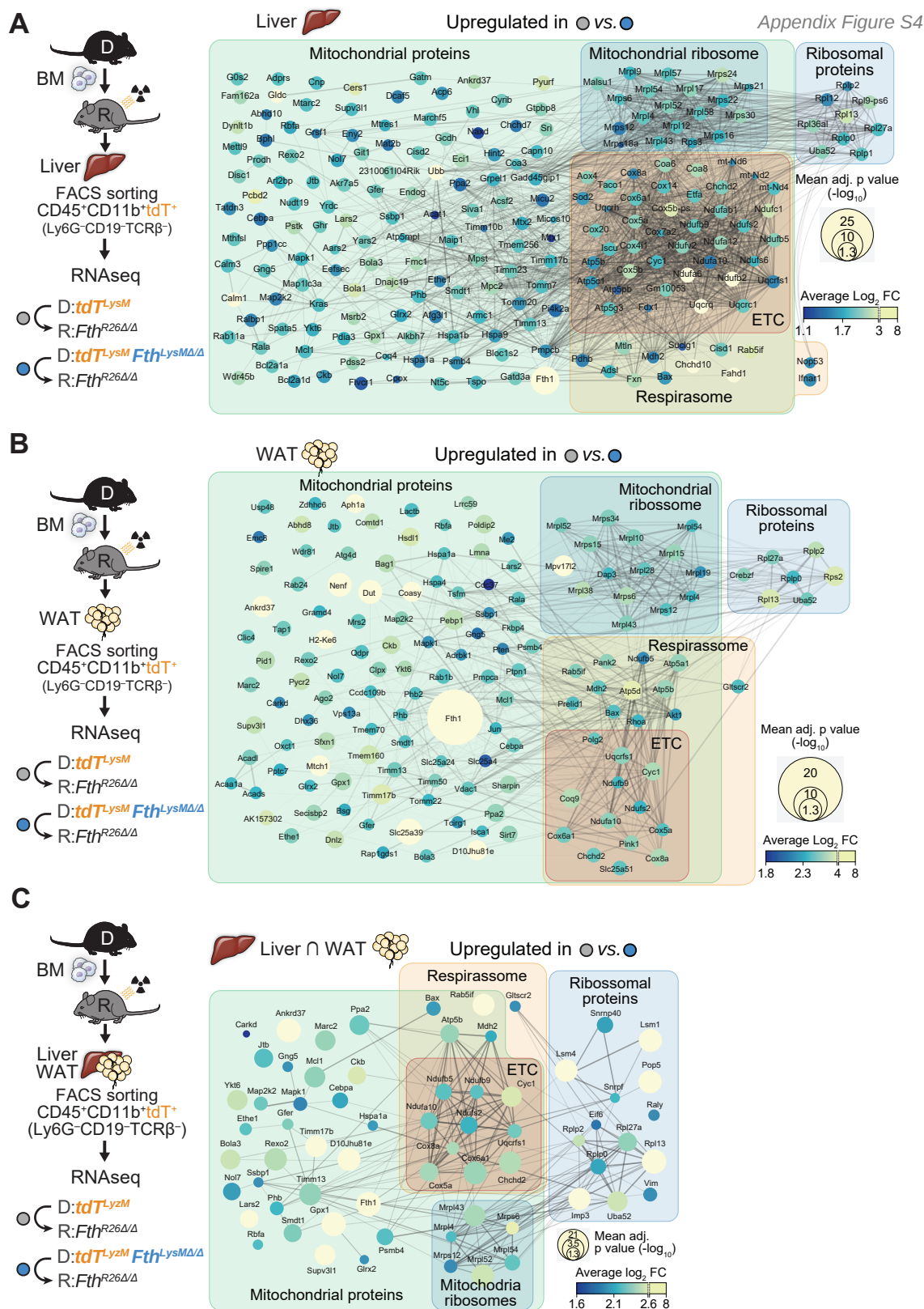
Appendix Figure S2: *Fth*-competent myeloid cells prevent the formation of iron-filled siderosomes in chimeric *Fth*-deleted mice. Schematic representation of chimeric mice and TAM-induced *Fth* deletion (day 0) and representative transmission electron microscopy images of siderosome-like structures present in **(A)** hepatocytes (liver) and **(B)** adipocytes (gWAT) from *Fth*^{R26Δ/Δ}⇒*Fth*^{R26Δ/Δ} chimeric mice, collected on

day 8 (early onset), and $Fth^{LysM\Delta/\Delta} \Rightarrow Fth^{R26\Delta/\Delta}$ chimeric mice, collected on day 30 (late onset), but absent in either $Fth^{fl/fl} \Rightarrow Fth^{fl/fl}$ or $Fth^{fl/fl} \Rightarrow Fth^{R26\Delta/\Delta}$ chimeric mice, at either time points. Red arrows indicate membrane-bound, electron-dense, siderosome-like structures filled with apparent crystalline iron, consistent with earlier descriptions (Sato, Ogihara et al., 1978). Yellow arrows indicate hepatic glycogen granules. Data in (A, B) is representative of 2 independent experiments with similar trends.



Appendix Figure S3: *Fth*-competent myeloid cells support tissue function in chimeric *Fth*-deleted mice. (A) Schematic representation of TAM-induced *Fth* deletion, cardiac function assessment and pressure volume loop analysis (PVA loop). (B) PVA loop analysis of *Fth^{fl/fl}* (n=7) and *Fth^{R26Δ/Δ}* (n=11) mice, on day 7 post-TAM administration. ESPVR = end systolic pressure-volume relationship, EDPVR = end diastolic pressure-volume relationship. (C) Schematic representation of TAM-induced *Fth* deletion (day 0) and cardiac function parameter quantification of *Fth^{fl/fl}* (n=7), *R26^{Cre}* (n=6) and *Fth^{R26Δ/Δ}* (n=11) mice, on

day 7 post-TAM administration. Data represented as individual values (circles) and mean (red bars). **(D)** Cardiac iron content in $Fth^{fl/fl} \Rightarrow Fth^{fl/fl}$ (n=3-5), $Fth^{R26\Delta/\Delta} \Rightarrow Fth^{R26\Delta/\Delta}$ (n=8) and $Fth^{fl/fl} \Rightarrow Fth^{R26\Delta/\Delta}$ (n=3-5) chimeric mice, 7 days (early onset) following TAM administration. Data pooled from 3 independent experiments with similar trends. **(E)** Schematic representation of chimeric mice and TAM-induced *Fth* deletion (day 0) and cardiac function parameters (end systolic pressure; preload recruitable stroke work; maximal power) in $Fth^{fl/fl} \Rightarrow Fth^{fl/fl}$ (n=4), $Fth^{R26\Delta/\Delta} \Rightarrow Fth^{R26\Delta/\Delta}$ (n=5), $Fth^{fl/fl} \Rightarrow Fth^{R26\Delta/\Delta}$ (n=5) and $Fth^{LysM\Delta/\Delta} \Rightarrow Fth^{R26\Delta/\Delta}$ (n=8) chimeric mice between days 10-51 following TAM administration. Data pooled from 2 independent experiments with similar trends. Data in (C-E) presented as individual values (circles) and mean (red bars). One-Way ANOVA with Tukey's range test for multiple comparison correction was used for comparison between multiple groups. NS: non-significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.



Appendix Figure S4: Mitochondrial gene expression program upregulated by *Fth*-competent monocyte-derived macrophages in *Fth*-deleted chimeras. (A-C) Schematic representations of chimeric mice, TAM administration and fluorescence-activated cell sorting (FACS) of *LySM*⁺

monocyte/macrophages (CD45⁺,CD11b⁺,Ly6G⁻,CD19⁻,TCRβ⁻) and STRING database (STRING-DB) interaction networks of mitochondrial, and mitochondria-related genes (as per gene ontology analysis) significantly upregulated in *LysM*⁺ monocyte-derived macrophages from *tdT^{LysM}⇒Fth^{R26Δ/Δ}* chimeric mice, as compared to *tdT^{LysM}Fth^{LysMΔ/Δ}⇒Fth^{R26Δ/Δ}* chimeric mice in either (A) liver or (B) WAT. (C) Mitochondrial and mitochondria-related genes that are significantly upregulated in *LysM*⁺ monocyte-derived macrophages from both the liver and WAT (intersection of significantly upregulated genes) of *tdT^{LysM}⇒Fth^{R26Δ/Δ}* chimeric mice, as compared to *tdT^{LysM}Fth^{LysMΔ/Δ}⇒Fth^{R26Δ/Δ}* chimeric mice. In (A-C), known interactions annotated in the STRING-DB are depicted by edges connecting gene dots.

Figure	Panel	Comparison				Note	Stars	p-value
1	D	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	***	0,0003	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	****	<0,0001	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	****	<0,0001	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$		$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	****	<0,0001	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	NS	0,273	
	F	$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Liver	**	0,0014	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Liver	***	0,0005	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Liver	NS	0,9656	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Liver	**	0,001	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Liver	***	0,0004	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Heart	NS	0,0807	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Heart	**	0,0012	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Heart	NS	0,1918	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Heart	*	0,0425	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Heart	***	0,0004	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Lungs	*	0,0104	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Lungs	**	0,0049	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Lungs	NS	0,9841	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Lungs	**	0,0094	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Lungs	**	0,0043	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Kidneys	***	0,0004	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Kidneys	*	0,0497	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Kidneys	NS	0,1795	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Kidneys	***	0,0003	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Kidneys	*	0,0495	
	G	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Parabiosis survival	NS	0,1119	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Parabiosis survival	***	0,0007	
		$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Parabiosis survival	**	0,0014	
		$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Parabiosis survival	NS	0,5165	
		$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Parabiosis survival	*	0,0294	
		$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Parabiosis survival	*	0,0376	
	I	$tdT^{R26} \rightarrow Fth^{fl/fl}$	VS.	$tdT^{R26} Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	**	0,0026	
		$tdT^{R26} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$tdT^{R26} Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	*	0,0203	
		$tdT^{R26} \rightarrow Fth^{fl/fl}$	VS.	$tdT^{R26} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	**	0,0021	
	J	$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Liver	***	0,0009	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Liver	****	<0,0001	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Liver	*	0,0395	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Spleen	**	0,008	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Spleen	*	0,0123	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Spleen	NS	0,924	
2	B	$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Early onset	****	<0,0001	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Early onset	**	0,0029	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Early onset	NS	0,079	
		$Fth^{wt/wt} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Late onset	****	<0,0001	
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta$						

G	Fth ^{fl/fl} → OKD48 ^{Luc} Fth ^{R26Δ/Δ}	VS.	Fth ^{R26MΔ/Δ} → OKD48 ^{Luc} Fth ^{R26Δ/Δ}	Early onset	*	0,0237
		VS.	Fth ^{wt/wt} → OKD48 ^{Luc} Fth ^{fl/fl}	Early onset	NS	0,9143
	Fth ^{wt/wt} → OKD48 ^{Luc} Fth ^{fl/fl}	VS.	Fth ^{LysMΔ/Δ} → OKD48 ^{Luc} Fth ^{R26Δ/Δ}	Late onset	**	0,0041
		VS.	Fth ^{fl/fl} → OKD48 ^{Luc} Fth ^{R26Δ/Δ}	Late onset	**	0,0065
	Fth ^{wt/wt} → OKD48 ^{Luc} Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → OKD48 ^{Luc} Fth ^{R26Δ/Δ}	Late onset	NS	0,6837
		VS.	Fth ^{fl/fl} → Fth ^{fl/fl}	Late onset	**	0,008
	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Late onset	*	0,0146
		VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Late onset	NS	0,9357
	Fth ^{wt/wt} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Heart rate	NS	0,9993
		VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Heart rate	NS	0,0819
		VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Heart rate	*	0,0219
		VS.	Fth ^{wt/wt} → Fth ^{fl/fl}	Mean arterial pressure	NS	0,8667
		VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Mean arterial pressure	*	0,0494
		VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Mean arterial pressure	**	0,0032

Figure	Panel	Comparison		Note	Stars	p-value
3	B	Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Light	****
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Light	****
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Light	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Dark	****
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Dark	****
	C	Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Dark	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Light	***
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Light	**
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Light	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Dark	****
	D	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Dark	***
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Dark	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Light	****
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Dark	****
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Dark	****
	E	Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Dark	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Light	****
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Light	****
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Light	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Dark	****
	F	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Dark	****
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Dark	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Light	***
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Light	***
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Dark	***
	G	Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Dark	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Light	**
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Light	**
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Light	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Dark	***

Figure	Panel	Comparison		Note	Stars	p-value
	B	Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	BAT	***
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	BAT	***
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	BAT	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Tail	NS
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Tail	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Tail	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Temperature delta	****
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{R26Δ/Δ} → Fth ^{R26Δ/Δ}	Temperature delta	****
	D	Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	Temperature delta	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	BAT	**
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	BAT	*
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	BAT	NS
		Fth ^{fl/fl} → Fth ^{fl/fl}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Tail	*
		Fth ^{fl/fl} → Fth ^{R26Δ/Δ}	VS.	Fth ^{LysMΔ/Δ} → Fth ^{R26Δ/Δ}	Tail	NS

4	F	$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	Tail	NS	0,5502
		$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{LysM\Delta/\Delta} \rightarrow F^{th}/^{R26\Delta/\Delta}$	Temperature delta	*	0,0217
		$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	vs.	$F^{th}/^{LysM\Delta/\Delta} \rightarrow F^{th}/^{R26\Delta/\Delta}$	Temperature delta	*	0,0385
		$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	Temperature delta	NS	0,9211
	F	$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{R26\Delta/\Delta} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - organ weight	****	<0,0001
		$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	vs.	$F^{th}/^{R26\Delta/\Delta} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - organ weight	****	<0,0001
		$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - organ weight	NS	0,5741
		$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{R26\Delta/\Delta} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - Adipocyte area	**	0,0072
		$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	vs.	$F^{th}/^{R26\Delta/\Delta} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - Adipocyte area	*	0,016
		$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - Adipocyte area	NS	0,8223
		$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{LysM\Delta/\Delta} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - organ weight	*	0,0205
		$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	vs.	$F^{th}/^{LysM\Delta/\Delta} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - organ weight	**	0,0057
	H	$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - organ weight	NS	0,8223
		$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{LysM\Delta/\Delta} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - Adipocyte area	*	0,0234
		$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	vs.	$F^{th}/^{LysM\Delta/\Delta} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - Adipocyte area	NS	0,0651
		$F^{th}/^{th} \rightarrow F^{th}/^{th}$	vs.	$F^{th}/^{th} \rightarrow F^{th}/^{R26\Delta/\Delta}$	gWAT - Adipocyte area	NS	0,958

G	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	MT-CO1	NS	0,1864
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	MT-CO1	NS	0,2435
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	MT-CyB	**	0,0017
	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	MT-CyB	**	0,0036
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	MT-CyB	NS	0,9798
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	PolG	**	0,0039
	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	PolG	***	0,0004
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	PolG	NS	0,5812
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Cs	**	0,0088
	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Cs	*	0,0435
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Cs	NS	0,827
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Nrf1	NS	0,3112
	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Nrf1	NS	0,2847
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	Nrf1	NS	0,9865
J	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	CI	NS	0,1952
	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	CI	*	0,0294
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	CI	NS	>0,9999
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	CII	*	0,0167
	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	CII	*	0,0166
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	CII	NS	>0,9999
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	CIV	*	0,0483
	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	CIV	NS	0,1021
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	CIV	NS	>0,9999
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	CIV	**	0,0055
	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	CIV	NS	0,394
	$Fth^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	CIV	NS	0,5044

Figure	Panel	Comparison		Note	Stars	p-value
7	F	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Liver - Ly6C ^{hi} PhAM MFI	***
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Liver - Ly6C ^{hi} % PhAM ⁺	*
	G	$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	WAT - Ly6C ^{hi} PhAM MFI	*
		$Fth^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	WAT - Ly6C ^{hi} % PhAM ⁺	*

Figure	Panel	Comparison		Note	Stars	p-value
8	A	$Tfam^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	*
		$Tfam^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	**
		$Tfam^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	NS
		$Tfam^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Tfam^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	*
		$Tfam^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Tfam^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	**
	B	$Uqcrcq^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	**
		$Uqcrcq^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	**
		$Uqcrcq^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Fth^{R26\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	**
		$Uqcrcq^{fl/fl} \rightarrow Fth^{fl/fl}$	VS.	$Uqcrcq^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	NS
		$Uqcrcq^{fl/fl} \rightarrow Fth^{R26\Delta/\Delta}$	VS.	$Uqcrcq^{LysM\Delta/\Delta} \rightarrow Fth^{R26\Delta/\Delta}$	Survival	>0,9999
	E	$PhAM^{R26}$	VS.	$PhAM^{LysM} \rightarrow tdT^{R26}$	Liver - CD45 ⁺ PhAM MFI	****
		$PhAM^{R26}$	VS.	$PhAM^{LysM} \rightarrow tdT^{R26} Fth^{R26\Delta/\Delta}$	Liver - CD45 ⁺ PhAM MFI	****
		$PhAM^{R26}$	VS.	$PhAM^{LysM} Fth^{LysM\Delta/\Delta} \rightarrow tdT^{R26} Fth^{R26\Delta/\Delta}$	Liver - CD45 ⁺ PhAM MFI	****
	H	$Fth^{fl/fl} \rightarrow PhAM^{R26}$	VS.	$Fth^{fl/fl} \rightarrow PhAM^{R26} Fth^{R26\Delta/\Delta}$	Liver - Ly6C ^{hi} PhAM MFI	NS
		$Fth^{fl/fl} \rightarrow PhAM^{R26}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow PhAM^{R26} Fth^{R26\Delta/\Delta}$	Liver - Ly6C ^{hi} PhAM MFI	***
		$Fth^{fl/fl} \rightarrow PhAM^{R26} Fth^{R26\Delta/\Delta}$	VS.	$Fth^{LysM\Delta/\Delta} \rightarrow PhAM^{R26} Fth^{R26\Delta/\Delta}$	Liver - Ly6C ^{hi} PhAM MFI	***
	K	$Fth^{fl/fl} + Vehicle$	VS.	$Fth^{R26\Delta/\Delta} + Mitochondria$	BMDM viability	**
		$Fth^{R26\Delta/\Delta} + Vehicle$	VS.	$Fth^{R26\Delta/\Delta} + Mitochondria$	BMDM viability	**
		$Fth^{fl/fl} + Mitochondria$	VS.	$Fth^{R26\Delta/\Delta} + Mitochondria$	BMDM viability	**
	L	$Fth^{fl/fl} + Vehicle$	VS.	$Fth^{R26\Delta/\Delta} + Iron$	BMDM viability	****
		$Fth^{R26\Delta/\Delta} + Vehicle$	VS.	$Fth^{R26\Delta/\Delta} + Iron$	BMDM viability	****
		$Fth^{fl/fl} + Iron$	VS.	$Fth^{R26\Delta/\Delta} + Iron$	BMDM viability	****

Appendix Table S1: Table containing the p-values and significance levels for the different statistical pairwise comparisons from Figures 1 to 8. Statistical analysis details are described in the respective figure legend, and in the “Statistical analysis” paragraph within the Methods section.