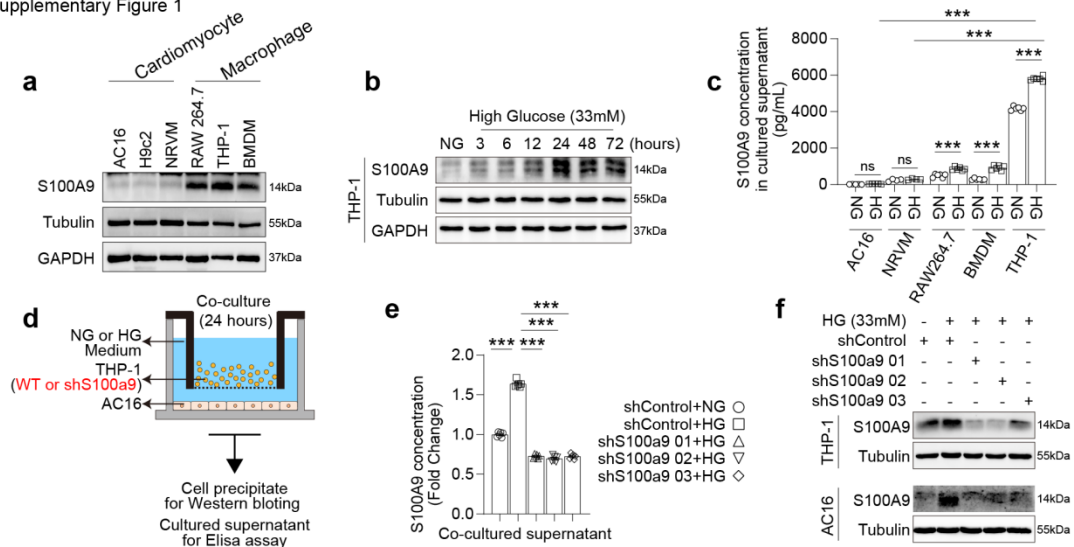


Supplementary Figure 1

Supplementary Figure 1

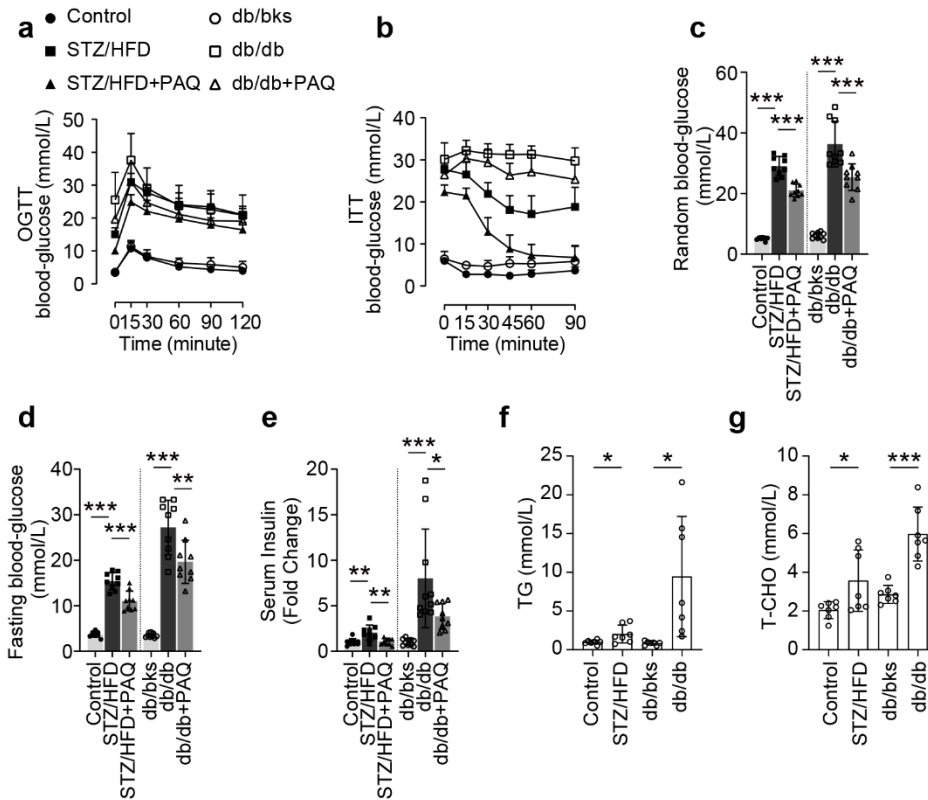


Supplementary Fig. 1 Differences in the expression and secretion of S100A9 in macrophages and cardiomyocytes.

a, S100A9 expression in macrophages and cardiomyocytes. **b**, S100A9 expression in THP-1 macrophages exposed to high glucose (33mM). **c**, S100A9 secretion in macrophages and cardiomyocytes exposed to high glucose (33mM). **d**, schematic diagram of co-cultured macrophages and cardiomyocytes. **e**, S100A9 level in co-cultured supernatant. **f**, S100A9 expression in co-cultured macrophages and cardiomyocytes. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. All data are presented as mean $\pm$ SD. Statistical significance was determined by one-way ANOVA.

13 **Supplementary Figure 2**

Supplementary Figure 2



14

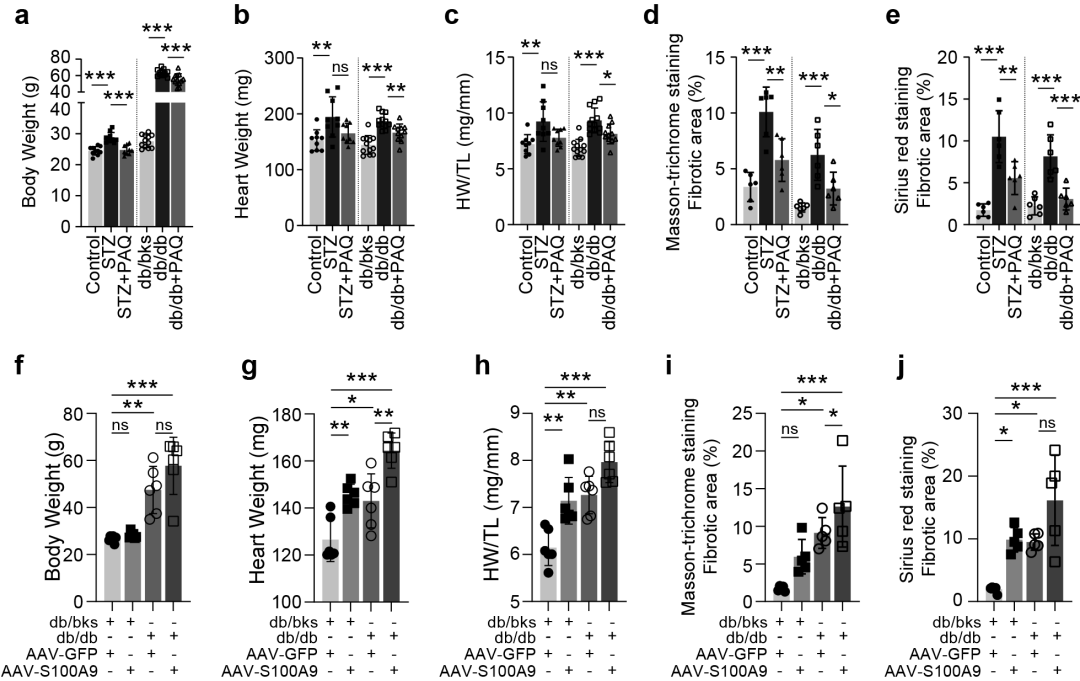
15

16 **Supplementary Fig. 2 Blood glucose and lipid levels in diabetic mice.**

17 **a**, OGTT (Oral Glucose Tolerance Test). **b**, ITT (Insulin Tolerance Test). **c**, random
 18 blood glucose. **d**, fasting blood glucose. **e**, insulin levels. **f**, total triglyceride (TG). **g**,
 19 total cholesterol (T-CHO). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. All data are presented
 20 as mean $\pm$ SD. Statistical significance was determined by unpaired student's t-test (2f,
 21 2g), or one-way ANOVA (2c-2e).

22 **Supplementary Figure 3**

Supplementary Figure 3



23

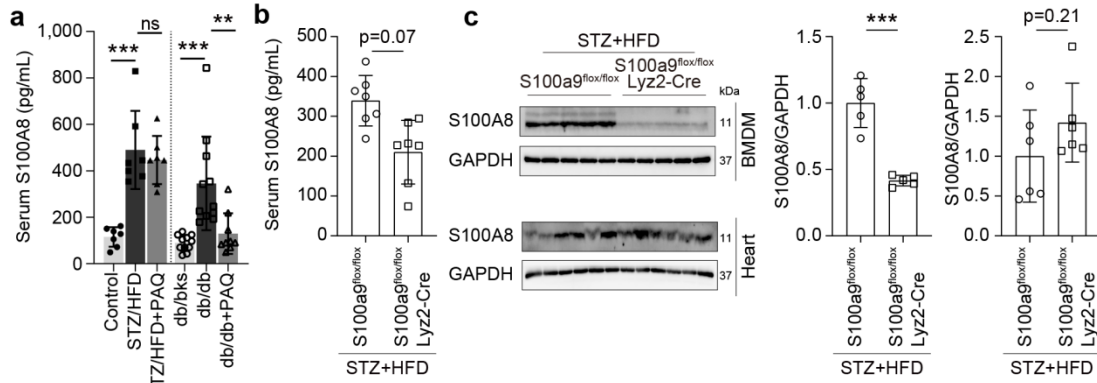
24

25 **Supplementary Fig. 3 Quantification of heart morphology and fibrosis.**

26 Quantification of body weight, heart weight (HW), HW/TL(tibial length),
 27 Masson-trichrome staining, and Sirius red staining in STZ/HFD-induced or db/db
 28 diabetic mice (a-e) and mice with cardiac-specific overexpression of S100A9 (f-j). * p
 29 < 0.05 , ** $p < 0.01$, *** $p < 0.001$. All data are presented as mean $\pm$ SD. Statistical
 30 significance was determined by one-way ANOVA.

Supplementary Figure 4

Supplementary Figure 4

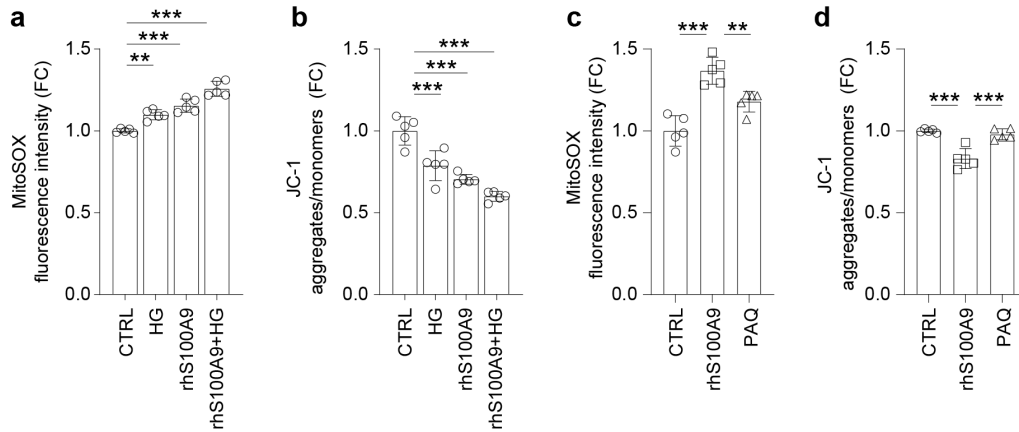


Supplementary Fig. 4 S100A8 expression in diabetic mice and macrophage specific S100a9 knockout mice.

a, Serum S100A8 concentration in diabetic mice (n=7, STZ group; n=9, db/db group).
b, Serum S100A8 concentration in macrophage specific S100a9 knockout mice (n=7).
c, S100A8 expression in BMDM (n=5) and heart (n=6) of macrophage specific S100a9 knockout mice. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. All data are presented as mean $\pm$ SD. Statistical significance was determined by unpaired student's t-test (4b-4c), or one-way ANOVA (4a).

42 **Supplementary Figure 5**

Supplementary Figure 5



43

44

45 **Supplementary Fig. 5 Quantification of MitoSOX and JC-1 staining in AC16**
 46 **cells.**

47 AC16 cells exposed to rhS100A9 (2μg/mL), high glucose (33mM), and/or
 48 paquinimod (PAQ, 20μM). **a** and **c**, MitoSOX staining. **b** and **d**, JC-1 staining. * $p <$
 49 0.05, ** $p <$ 0.01, *** $p <$ 0.001. All data are presented as mean $\pm$ SD. Statistical
 50 significance was determined by one-way ANOVA.

51