Supplemental Figure 1. Mutant and control mice demonstrate equal size injury region at 2 days post-LAD ligation. (A, B) Whole-mount images and histology of control (n=3) and mutant animals (n=4) as indicated, 2 days post-MI (LAD ligation). White dotted line demarcates area of injury near the ligature, and representative Trichrome staining of sections at base (i), mid-ventricle (ii), and apex (iii). (C) Quantification of fibrosis of serial sections; there is no statistical difference between fibrosis in mutant and control (P value was calculated using a two-tailed Student’s t-test; Data represent mean ± SEM) (D, E) Whole-mount images and histology of control (n=3) and mutant (n=3) 14 days after sham surgery. No excessive fibrosis is noted in the chest wall cavity or heart in the mutant (E). Representative histology images from base, mid-ventricle, and apex are shown in (D, E). (A-E) Tamoxifen administered to both control and mutant 2 days prior to and 2 days post surgery. Scale Bars: 1 mm.
Supplemental Figure 2. Cardiac function in epicardial null mice and control mice are the same at baseline. Transthoracic echocardiography in 3 control (Taz^{flax/flox}; Yap^{flox/flox}) and 3 mutant mice (Wt1^{CreERT2/}; Yap^{flox/flox}; Taz^{flox/flox}) after tamoxifen induction and no surgery at 1 week post-MI shows no significance difference in body weight (A), left ventricular end-diastolic volume (LV EDV) (B), stroke volume (C), and cardiac output (D). Data represent mean ± SD. P values were calculated using a two-tailed Student’s t-test. Significance: N.S. = not significant.
Supplemental Figure 3. Epicardial Yap/Taz null mice demonstrate alteration of multiple immune targets at 14 days post-MI. (A) Bar graph of quantitative RT-PCR immune arrays from microdissected free LV walls of control (Yap^{flox/flox}; Taz^{flox/flox}, n=3) and mutant (Wt1^{CreERT2/+}; Yap^{flox/flox}; Taz^{flox/flox}, n=3) animals at 14 days post-MI. Red targets represent significantly downregulated genes in mutants compared with controls (n=3 in both groups). (B) Bar graph showing specific fold changes for the 10 significantly modulated genes in the qRT-PCR immune arrays (n=3 in both groups). Statistics were completed using a Student’s t-test. Data represent mean ± SD. Significance: *p < 0.05.
Supplemental Figure 4. IFN-γ is produced by epicardial activated cells after MI injury. Cross sections from Wt1^CreERT2^+/Yap^flox/flox^; Taz^flox/flox^; R26^Tomato/+^ animals following RNAscope in situ hybridization for IFN-γ 3 days after MI injury or sham surgery, as indicated (2 examples each). Black arrows denote IFN-γ positive cells in the epicardium, and white arrows denote corresponding tomato positive cells in the epicardium. Adjacent sections stained for Hoechst, Tomato or merged (Hoechst/Tomato) are shown as indicated. Scale bar: 25 μm.
Supplemental Figure 5. Epicardial Yap/Taz null mice exhibit a hyperinflammatory response. (A) Cross sections from Yap$^{flox/flox}$, Taz$^{flox/flox}$ (control) and Wt1CreERT2/+; Yap$^{flox/flox}$, Taz$^{flox/flox}$ (mutant) animals 14 days post-MI immunostained for CD4 and/or Hoechst demonstrating a similar number of CD4+ T-cells in both groups. (B) Cross sections from Yap$^{flox/flox}$, Taz$^{flox/flox}$ (control) and Wt1CreERT2/+; Yap$^{flox/flox}$, Taz$^{flox/flox}$ (mutant) animals 14 days post-MI immunostained for F4/80 and/or showing increased F4/80+ macrophages in the mutant mice compared to controls. Scale bars: 50 µm (A, B; top panels for each genotype), 25 µm (A, B; bottom panels for each genotype).
Supplemental Figure 6. Immune cell populations of the spleen and mediastinal lymph node are unchanged following epicardial Yap/Taz deletion. (A-B) Flow cytometry analyses of mediastinal lymph nodes and spleen 3 (A) and 14 (B) days post-MI from mutant (Wt1\textsuperscript{CreERT2/+}; Yap\textsuperscript{flx/flx}; Taz\textsuperscript{flx/flx}) and control (Yap\textsuperscript{flx/flx}; Taz\textsuperscript{flx/flx}) mice (n=3 in all analyses). Statistics were completed using a Student’s t-test, Data represent mean ± SD. Significance: # p < 0.10, and *p < 0.05.
Supplemental Table 1. Quantitative echocardiographic measurements demonstrate significantly reduced LV end-diastolic volume and chamber length in mutant mice after MI. Comprehensive echocardiographic measurements in Taz<sup>flox/flox</sup>; Yap<sup>flox/flox</sup> (control, n=7) and Wt1<sup>CreERT2/</sup> <sup>+</sup>; Yap<sup>flox/flox</sup>, Taz<sup>flox/flox</sup> (mutant, n=6) animals one week post-MI show significantly reduced LV end-diastolic volume, LV diastolic endocardial length and LV systolic endocardial length in epicardial Yap/Taz null mice. Means and standard deviations are shown for each corresponding metric. P values were calculated using a two-tailed Student’s t-test.

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**LEGEND**
- **BW** grams: Body weight
- **HR** bpm: Heart rate
- **LVAEpid** mm<sup>2</sup>: LV epicardial area at end diastole
- **LVAENDd** mm<sup>2</sup>: LV endocardial area at end diastole
- **LVAENDs** mm<sup>2</sup>: LV endocardial area at end systole
- **LVLd** mm: LV length from plane of the mitral valve to the apical endocardial surface during diastole
- **LVLs** mm: LV length from plane of the mitral valve to the apical endocardial surface during systole
- **EDV** ul: End diastolic LV volume
- **ESV** ul: End systolic LV volume
- **SV** ul: Stroke volume
- **CO** ml/min: Cardiac output
- **IVSd** mm: Thickness of the Interventricular septum in diastole
- **IVSs** mm: Thickness of the Interventricular septum in systole
- **LVPWd** mm: LV posterior wall thickness, diastole
- **LVPWs** mm: LV posterior wall thickness, systole
- **LVIDd** mm: LV dimension in diastole
- **LVIDs** mm: LV dimension in systole