Supporting information

**UVRAG Deficiency Exacerbates Doxorubicin-Induced Cardiotoxicity**

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Figure S1. UVRAG expression in the hearts from WT and UVRAG-deficient mice after vehicle and DOX treatment. (a) Western blot detection of UVRAG protein abundance in LVs from WT and UVRAG-deficient mice 5 days after acute DOX or vehicle treatment. (b) Western blot detection of UVRAG protein abundance in LVs from WT and UVRAG-deficient mice at 4 weeks of chronic DOX or vehicle treatment.
Figure S2. Expression of α-SMA in the hearts from WT and UVRAG-deficient mice after acute DOX and vehicle treatment. (a) Representative images of α-SMA immunohistochemistry in LVs on heart sections from WT and UVRAG-deficient mice after chronic DOX or vehicle treatment over the indicated time. Scale bar: 40 μm. (b) Quantification of α-SMA expression in LVs in the experiments as illustrated in (a). n=3 mice for each group. *P<0.05 vs. WT+vehicle, #P<0.05 vs. WT+DOX.

Figure S3. Expression of α-SMA in the hearts from WT and UVRAG-deficient mice after chronic DOX and vehicle treatment. (a) Representative images of α-SMA immunohistochemistry in LVs on heart sections from WT and UVRAG-deficient mice after chronic DOX or vehicle treatment over the indicated time. Scale bar: 40 μm. (b) Quantification of α-SMA expression in LVs in the experiments as illustrated in panel (a). n=3 mice for each group. *P<0.05 vs. WT+vehicle, #P<0.05 vs. WT+DOX.
Figure S4. Representative images of apoptotic cells detected by TUNEL assay. Scale bar: 40 µm.

Figure S5. Assessment of inflammatory cytokines in acute and chronic DOX-induced cardiotoxicity. (a) TNFα levels in the hearts from WT and UVRAG-deficient mice 3 days after vehicle or DOX treatment. (b) TNFα levels in the hearts from WT and UVRAG-deficient mice at 2 weeks of chronic DOX or vehicle treatment. (c) IL-6 levels in the hearts from WT and UVRAG-deficient mice 3 days after vehicle or DOX treatment. (d)
IL-6 levels in the hearts from WT and UVRAG-deficient mice at 2 weeks of chronic DOX or vehicle treatment. (e) IL-1β levels in the hearts from WT and UVRAG-deficient mice 3 days after vehicle or DOX treatment. (f) IL-1β levels in the hearts from WT and UVRAG-deficient mice at 2 weeks of chronic DOX or vehicle treatment. n=4 mice for each group. *P<0.05 vs. WT+vehicle. # P<0.05 vs. WT+DOX.

Figure S6. Beclin 1 and Atg5 expression in the hearts from WT and UVRAG-deficient mice after vehicle and DOX treatment. (a) Western blot detection of Beclin 1 protein abundance in LVs from WT and UVRAG-deficient mice 3 days after acute DOX or vehicle treatment. (b) Quantification of Beclin 1 as illustrated in panel (a). (c) Western blot detection of Atg5 protein abundance in LVs from WT and UVRAG-deficient mice 3 days after acute DOX or vehicle treatment. (d) Quantification of Atg5 as illustrated in panel (c). (e) Western blot detection of Beclin 1 protein abundance in LVs from WT and UVRAG-deficient mice at 4 weeks of chronic DOX or vehicle treatment. (f) Quantification
of Beclin 1 as illustrated in panel (e). (g) Western blot detection of Atg5 protein abundance in LVs from WT and UVRAG-deficient mice at 4 weeks of chronic DOX or vehicle treatment. (h) Quantification of Atg5 as illustrated in panel (g). *P<0.05 vs. WT+vehicle, #P<0.05 vs. UVRAG−/−vehicle, §P<0.05 vs. WT+DOX.

Figure S7. Effects of intermittent fasting on lysosomal markers in acute cardiotoxicity. (a) Representative images of immunohistochemistry for LAMP-1 in LVs on the heart sections from fed or fasted WT and UVRAG-deficient mice 5 days after acute DOX or vehicle treatment. (b) Representative images of immunohistochemistry for LAMP-2 in LVs on the heart sections from fed or fasted WT and UVRAG-deficient mice 5 days after acute DOX or vehicle treatment. Scale bar: 40 μm.
Figure S8. Effects of intermittent fasting on lysosomal markers in chronic cardiotoxicity.

(a) Representative images of immunohistochemistry for LAMP-1 in LVs on the heart sections from fed or fasted WT and UVRAG-deficient mice 4 weeks after the initial DOX treatment in chronic cardiotoxicity. (b) Representative images of immunohistochemistry for LAMP-2 in LVs on the heart sections from fed or fasted WT and UVRAG-deficient mice 4 weeks after the initial DOX treatment in chronic cardiotoxicity. Scale bar: 40 μm.