

Supporting information

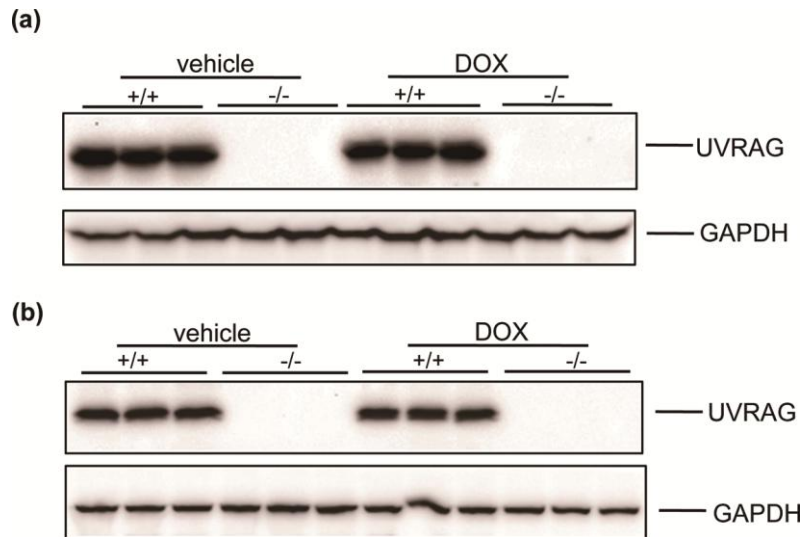
**UVRAG Deficiency Exacerbates Doxorubicin-Induced Cardiotoxicity**

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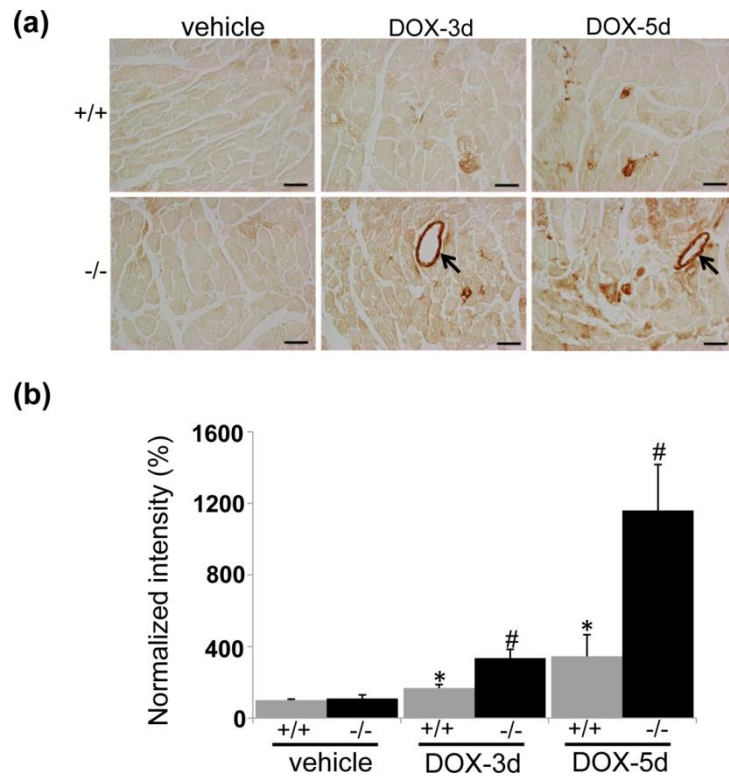
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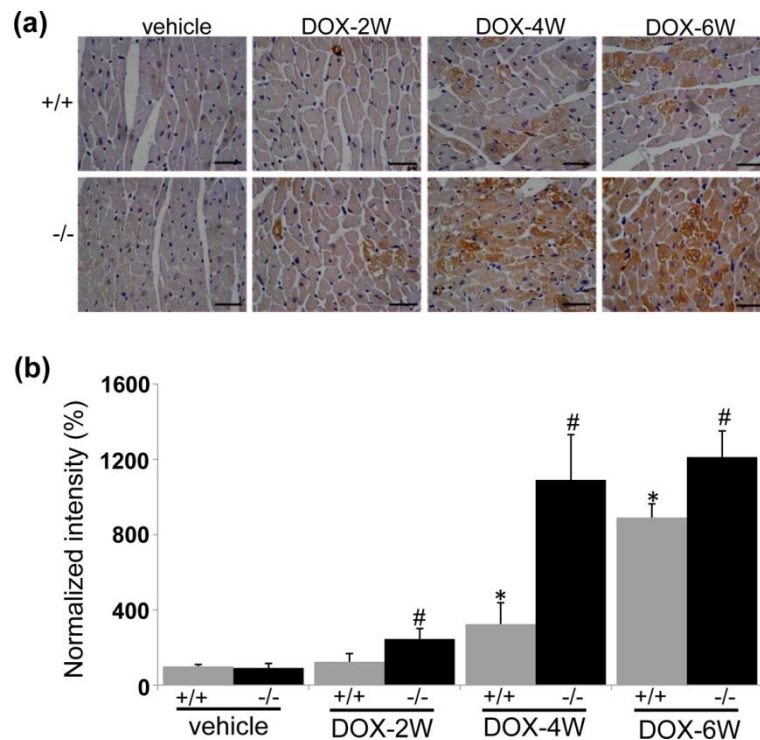
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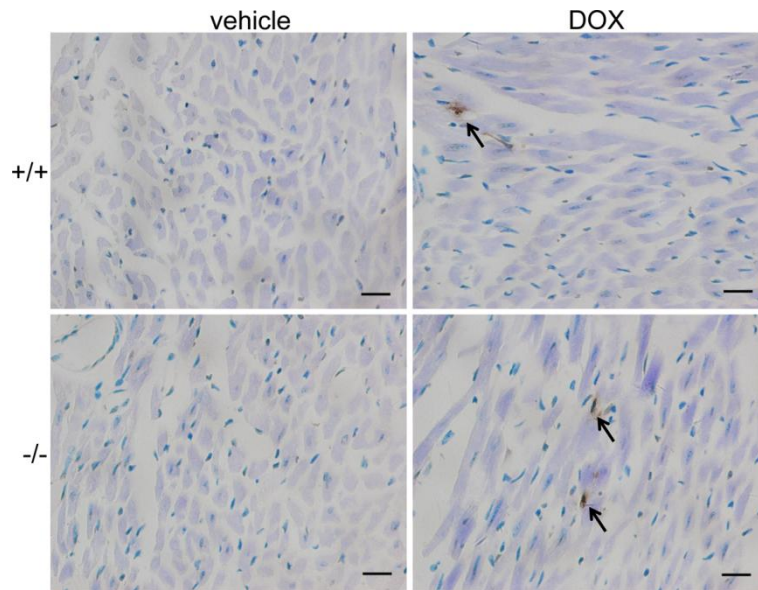
**Figure S1. UVRAG expression in the hearts from WT and UVRAG-deficient mice after vehicle and DOX treatment.** (a) Western blot detection of UVRAG protein abundance in LVs from WT and UVRAG-deficient mice 5 days after acute DOX or vehicle treatment. (b) Western blot detection of UVRAG protein abundance in LVs from WT and UVRAG-deficient mice at 4 weeks of chronic DOX or vehicle treatment.



**Figure S2. Expression of  $\alpha$ -SMA in the hearts from WT and UVRAG-deficient mice after acute DOX and vehicle treatment. (a)** Representative images of  $\alpha$ -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  $\mu$ m. **(b)** Quantification of  $\alpha$ -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.

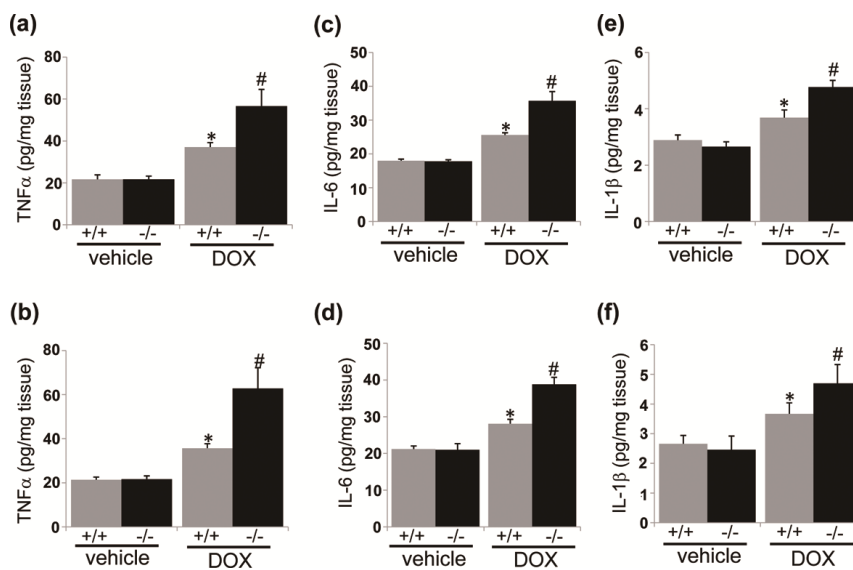


**Figure S3. Expression of  $\alpha$ -SMA in the hearts from WT and UVRAG-deficient mice after chronic DOX and vehicle treatment. (a)** Representative images of  $\alpha$ -SMA immunohistochemistry in LVs on heart sections from WT and UVRAG-deficient mice after chronic DOX or vehicle treatment over the indicated time. Scale bar: 40  $\mu$ m. **(b)** Quantification of  $\alpha$ -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.



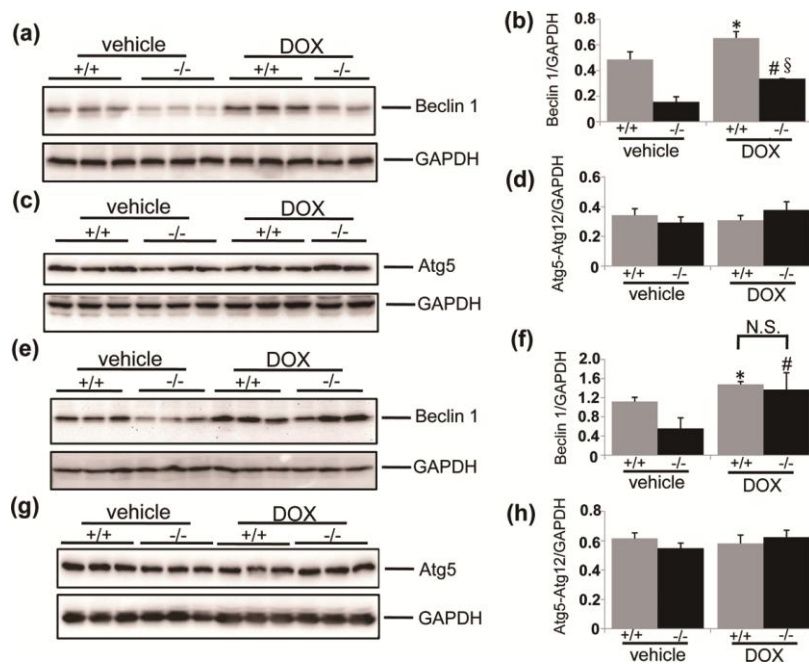
**Figure S4.** Representative images of apoptotic cells detected by TUNEL assay. Scale bar:

40  $\mu$ m.



**Figure S5.** Assessment of inflammatory cytokines in acute and chronic DOX-induced cardiotoxicity. **(a)** TNF $\alpha$  levels in the hearts from WT and UVRAG-deficient mice 3 days after vehicle or DOX treatment. **(b)** TNF $\alpha$  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)**

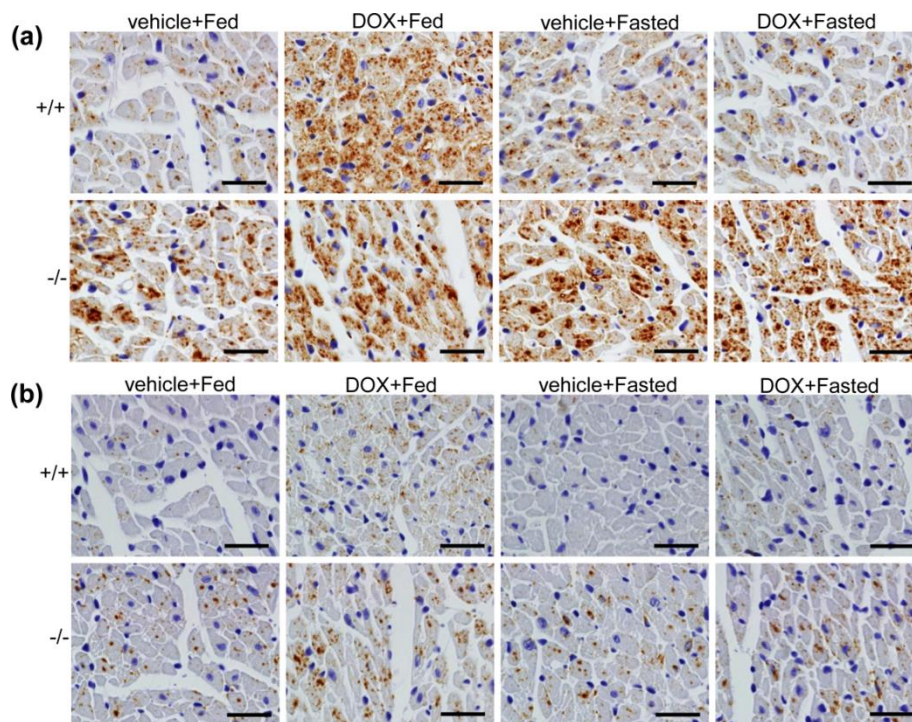
IL-6 levels in the hearts from WT and UVRAG-deficient mice at 2 weeks of chronic DOX or vehicle treatment. **(e)** IL-1 $\beta$  levels in the hearts from WT and UVRAG-deficient mice 3 days after vehicle or DOX treatment. **(f)** IL-1 $\beta$  levels in the hearts from WT and UVRAG-deficient mice at 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.



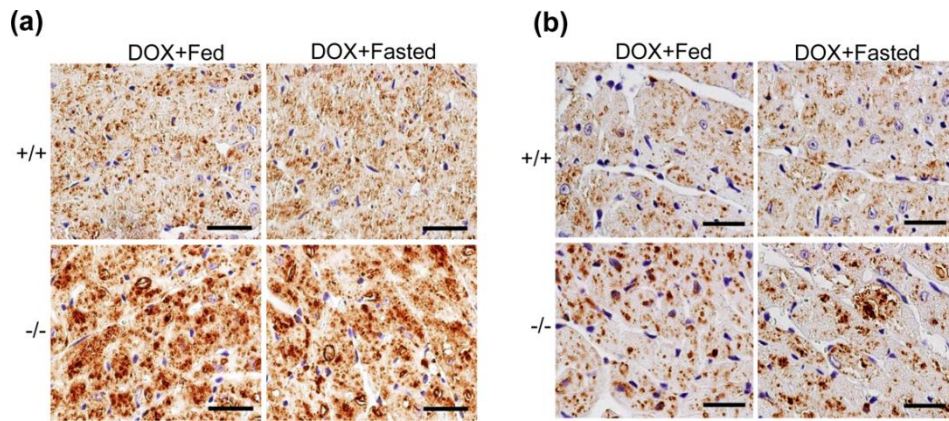
**Figure S6. Beclin 1 and Atg5 expression in the hearts from WT and UVRAG-deficient mice after vehicle and DOX treatment. (a)** Western blot detection of Beclin 1 protein abundance in LVs from WT and UVRAG-deficient mice 3 days after acute DOX or vehicle treatment. **(b)** Quantification of Beclin 1 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<sup>-/-</sup>+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  $\mu\text{m}$ .



**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  $\mu\text{m}$ .