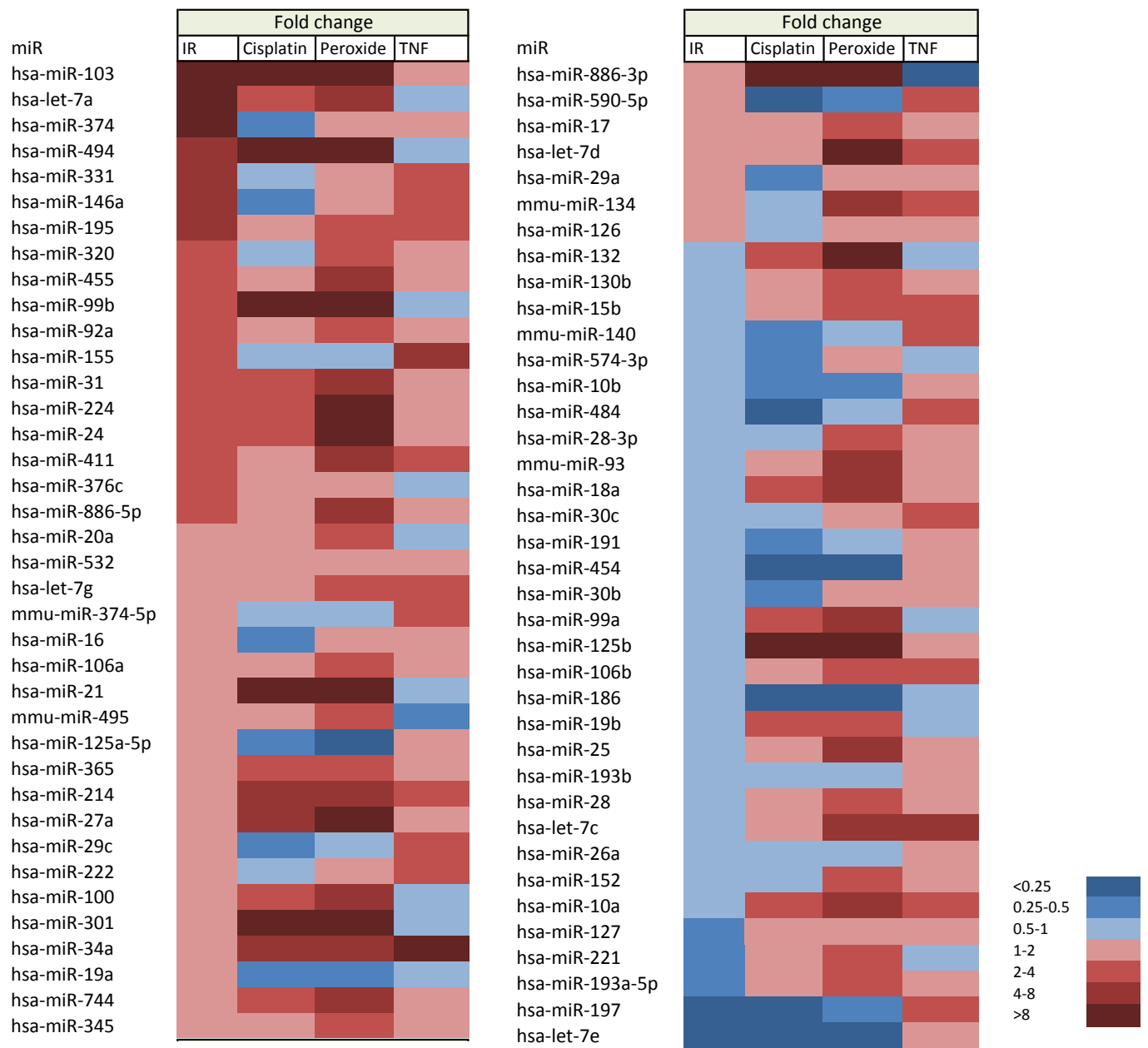


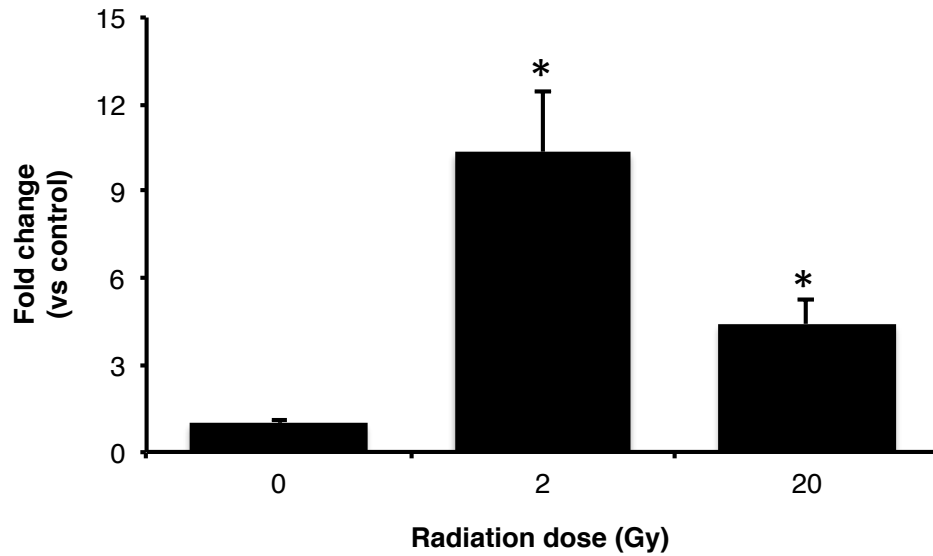
**Supplementary Figure 1. Loss of Dicer increases EC DNA damage.**

Comet assays of HUVECs with knockdown of DICER and indicated doses of radiation. Bottom panels depict mean+SEM of tail length and % of cells with tails.

\*  $P < 0.05$ , two-tailed Student's T-test.

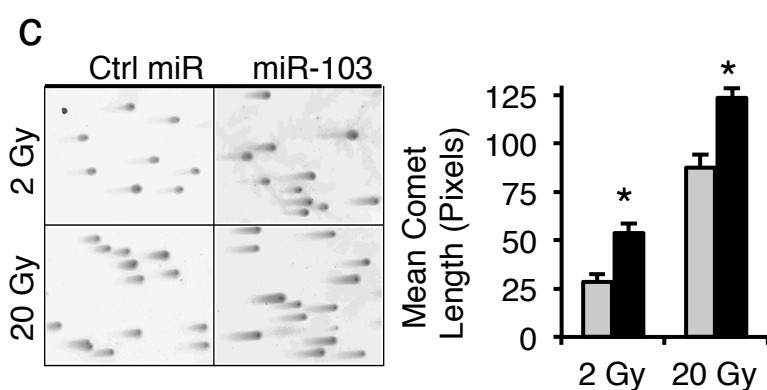
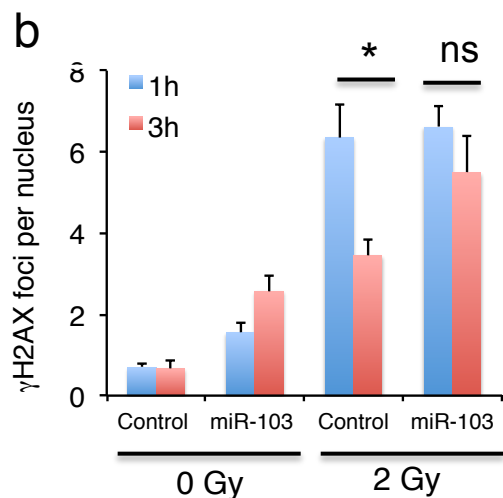
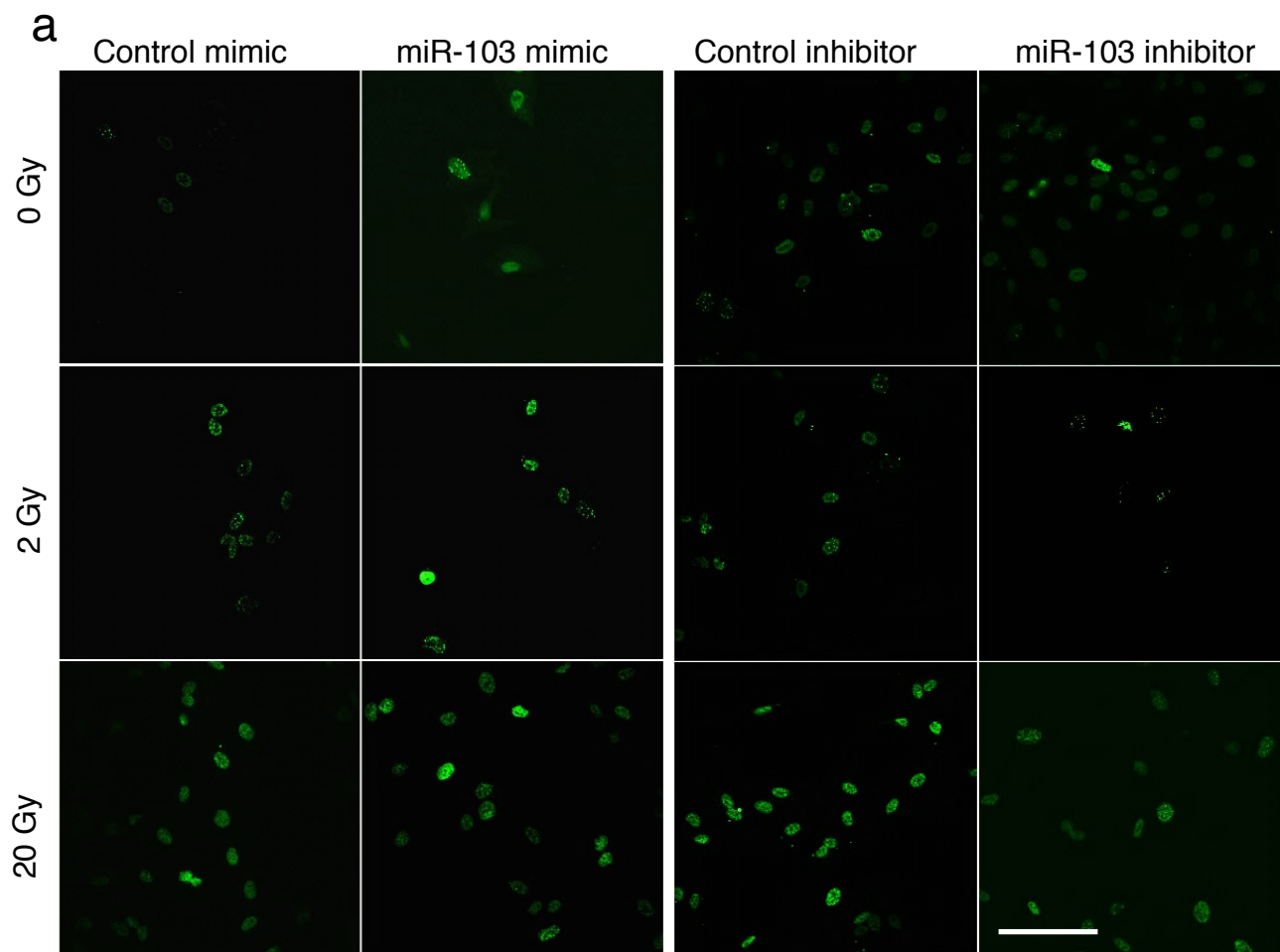


**Supplementary Figure 2. Heatmap showing the expression levels of miRNAs in HUVECs treated with different apoptotic agents.**



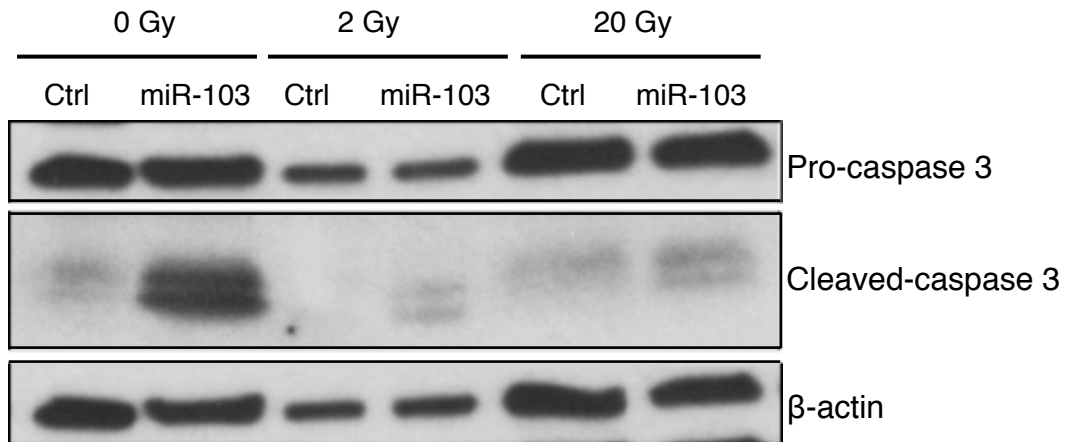
**Supplementary Figure 3. Mature miR-103 is induced by both low and high dose radiation.**

qRT-PCR of mature miR-103 from HUVECs 1h after the indicated doses of radiation. Mean+SEM of fold change over control is depicted. One of three independent experiments is shown. \*  $P < 0.05$ , student's T-test.



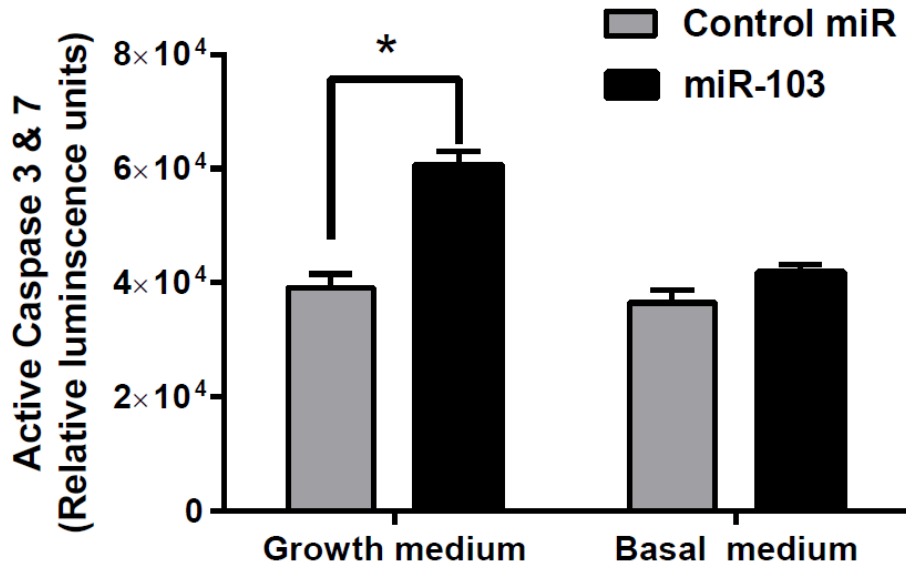
### Supplementary Figure 4. miR-103 induces DNA ds breaks in HUVECs

a) Representative immunofluorescence images corresponding to Fig 1g and 1h showing  $\gamma$ H2AX foci in HUVECs transfected with the indicated small RNAs treated with either 2 or 20 Gy radiation. These images represent DNA damage 3h post radiation. Scale bar = 100  $\mu$ m. b) Quantitation of foci for mimics c) A neutral comet assay depicting DNA ds breaks treated with the indicated doses of radiation 24h after ectopic expression of miR-103. Right panel bars show quantification of mean comet lengths from at least 5 different fields. All bars show mean + SEM. \*  $P < 0.05$ , Student's T-test



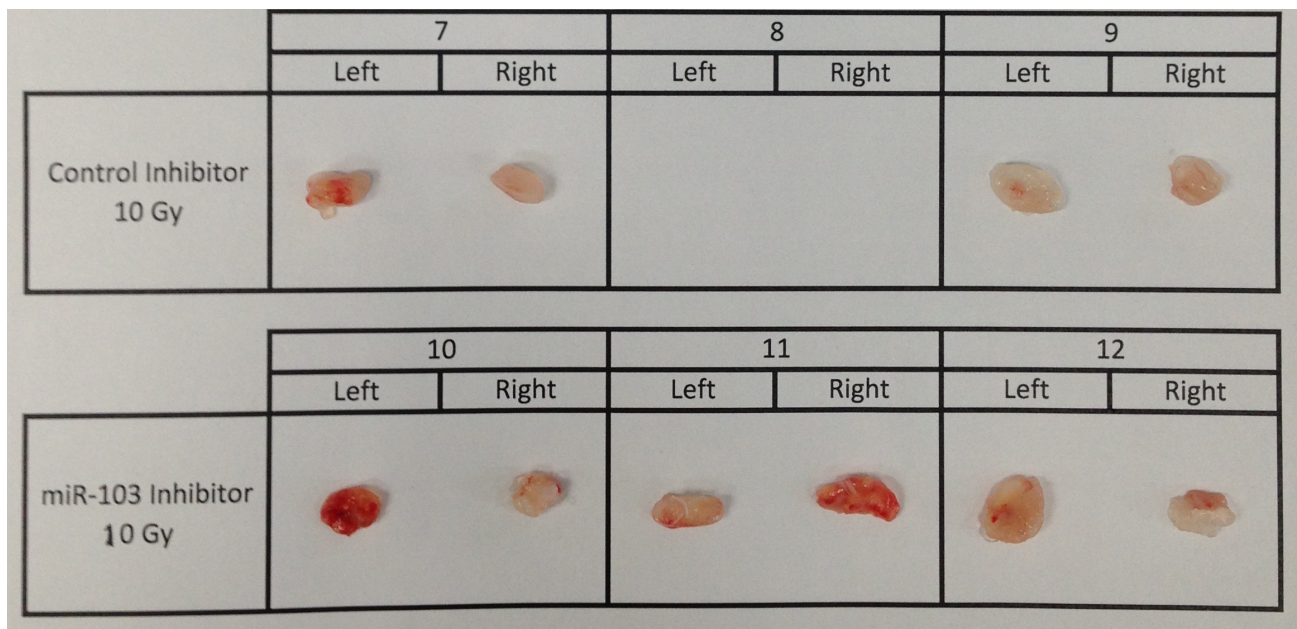
**Supplementary Figure 5. Expression of miR-103 activates caspase-3.**

HUVECs were transfected with either control mimic or miR-103 mimic for 24h and irradiated at the indicated doses. Caspase-3 activation was analyzed by western blot 24h after irradiation.

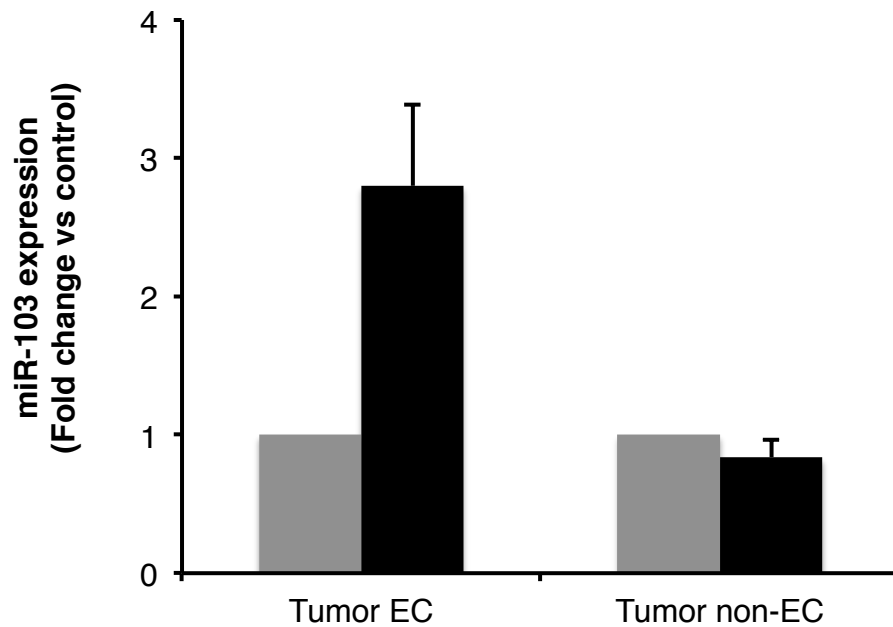


**Supplementary Figure 6. miR-103 affects proliferating but not quiescent ECs**

HUVECs were transfected with either control mimic or miR-103 mimic and maintained in either regular growth medium with 10% FBS and all growth factors (EGM2 with bullet kit, Lonza) or maintained in basal medium with 1% FBS and no growth factors. Active caspase levels were analyzed by a Caspase-Glo luminescence assay (Promega). Bars show mean + SEM. \*  $P < 0.05$ , Student's T-test.



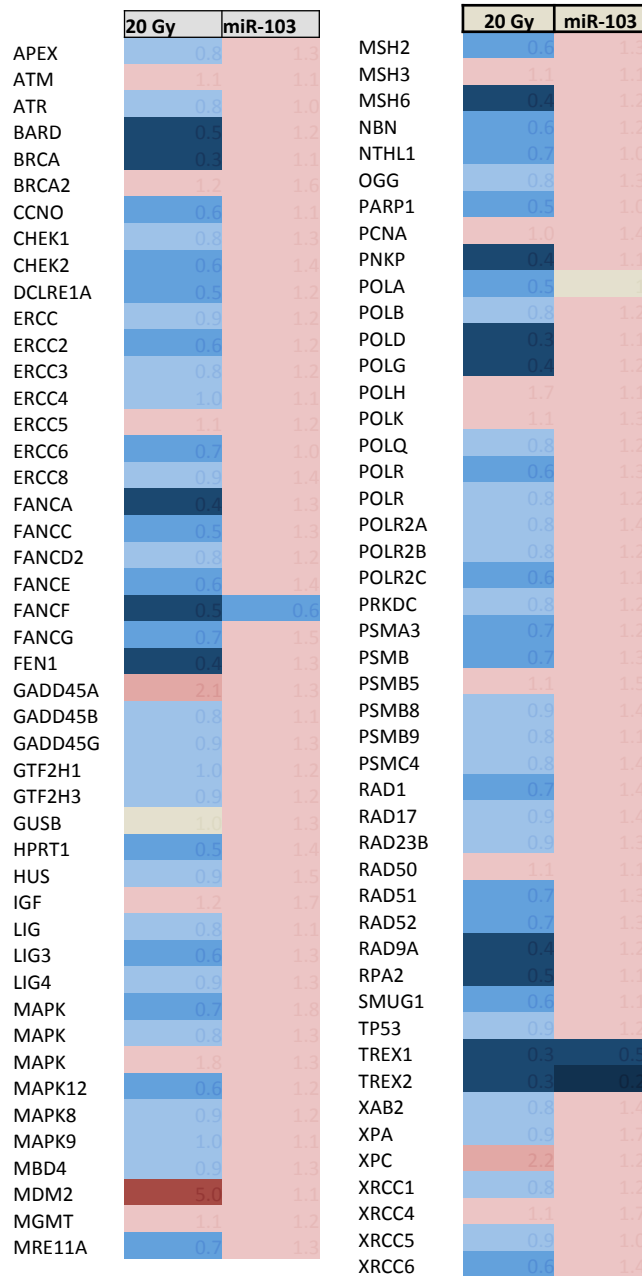
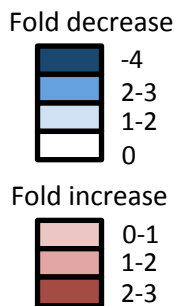
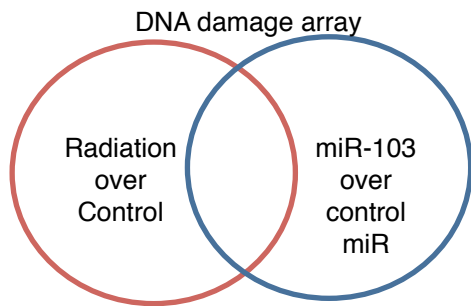
**Supplementary Figure 7. Representative images of Matrigel plugs from Fig 2e.**  
One of two representative experiments is shown.



**Supplementary Figure 8. 7C1 nanoparticles deliver miR cargo to tumor ECs.**

miR expression using qRT-PCR of RNA isolated from the endothelial vs non endothelial cell fractions of an HCT116 tumor suspension. Bars show mean + SEM.





**Supplementary Figure 9. Unbiased screen for miR-103 targets in DNA damage pathways.**

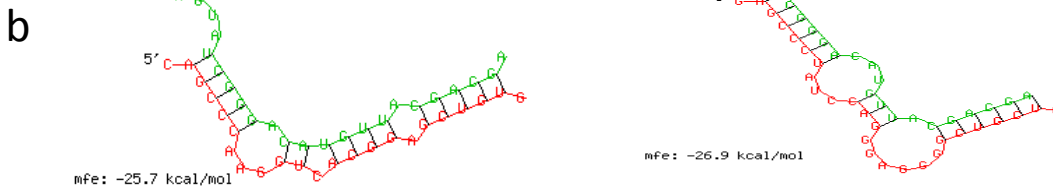
Heat maps of a DNA damage qPCR array showing normalized mRNA expression levels in HUVECs 24h after treatment with radiation or transfection with miR-103. The fold change levels are calculated over control or mock treated cells.

**a**

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      atg g g c t   c g c a g g c c c t   g c c c c g g g g   c c c a t g c a g a   c c c t c a t c t t
841 t t t c g a c a t g   g a g g c c a c t g   g c t t g c c c t t   c t c c   g a g c c c   a a g g t c a c g g   a g c t g t g c c t
901 g c t g g c t g t c   c a c a g a t g t g   c c c t g g a g a g   c c c c c c a c c   t e t c a g g g g c   c a c c t c c c a c
961 a g t t c c t c c a   c c a c c g c g t g   t g g t a g a c a a   g c t c t c c c t g   t g t g t g g c t c   c g g g g a a g g c
1021 c t g c a g c c c t   g c a g c c a g c g   a g a t c a c a g g   t e t g a g c a c a   g c t g t g c t g g   c a g c g c a t g g
1081 g c g t c a a t g t   t t t g a t g a c a   a c c t g g c c a a   c c t g c t c c t a   g c c t t c c t g c   g g c g c c a g c c
1141 a c a g c c c t g g   t g c c t g g t g g   c a c a c a a t g g   t g a c c g c t a c   g a c t t c c c c c   t g c t c c a a g c
1201 a g a g c t g g c t   a t g c t g g g c c   t c a c c a g t g c   t e t g g a t g g t   g c c t t c t g t g   t g g a t a g c a t
1261 c a c t g c g c t g   a a g g c c c t g g   a g c g a g c a a g   c a g c c c c t c a   g a a c a c g g c c   c a a g g a a g a g
1321 c t a c a g c c t a   g g c a g c a t c t   a c a c t c g c c t   g t a t g g g c a g   t c c c c t c c a g   a c t c g c a c a c
1381 g g c t g a g g g t   g a t g t c c t g g   c c c t g c t c a g   c a t c t g t c a g   t g g a g a c c a c   a g g c c c t g c t
1441 g c g t g g g t g   g a t g t c a c g   c c a g g c c t t t   c g g c a c c a t c   a g g c c c a t g t   a t g g g g t c a c
1501 a g c c t c t g c t   a g g a c c a a g c   c a a g a c c a t c   t g c t g t c a c a   a c c a c t g c a c   a c c t g g c c a c
1561 a a c c a g g a a c   a c t a g t c c c a   g c c t t g g a g a   g a g c a g g g g t   a c c a a g g a t c   t t c c t c c a g t
1621 g a a g g a c c c t   g   g a g c c c t a t   c c a g g g a g g g   g c t g c t g   c c c a c t g g g t c   t g c t g g c c a t
1681 c c t g a c c t t g   g c a g t a g c c a   c a c t g t a t g g   a c t a t c c c t g   g c c a c a c c t g   g g g a g   t a g g c
1741 c a a g a a g g a a   a a t c t g a c g a   a t a a a g a c c c   c g c t g c c c c   a t a a a a a a a a   a a a a a a a a a a
1801 a a a a a a a a a a   a a a a a a a a a a   a

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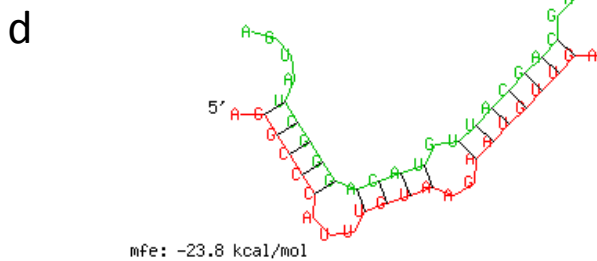


**c**

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1141 c c t c a g t t c t   g t a   t a g g   c a a   t g c t g t g t t a   t t a c t t g a a t   a t a g a a t a t a   t a g t t t a c a a
1201 a a t g a a a a t t   a c a a t g t t c t   c a c c a a a t a t   a t g c c t t c g t   g t g t c c a a a g   t a t a a t t a t t
1261 t t a g a t g c t a   a t t t t g a a t a   g t t t a t t a a a   c a g t t a t a a a   t a t g c a a a g t   a g c t g g c a t g
1321 t a g t g t c a c g   g a t t t t c t g g   a t a g a g g a a g   t g a t t g g a a g   t a c t c c a c t t   a a a g c c a t g g
1381 a a t t a g c a a t   a g t t t g c t t t   t t a a t a g a a g   g c c c a t t t g t   a a g a a t g t t g   a a a a t a t g t g
1441 t a c c g t t t a a   a g a a a a a g c a   g c t t t a a a g t   g a c a a a c a a a   a t a c c t t t t t   t c t t t t a g t a
1501 t g g t t t a t t t   t t c t a g t t t t   t e t g t c c c t c   c c t c a g t a g t   g a a g a g t t t t   c t t t a t t c c t
1561 g g c a g t g t c a   g g a a t a t t g g   t t t g a a a a g c   t g t t g g c c t a   t e t g g a g t t t   g g c c t t g t t a

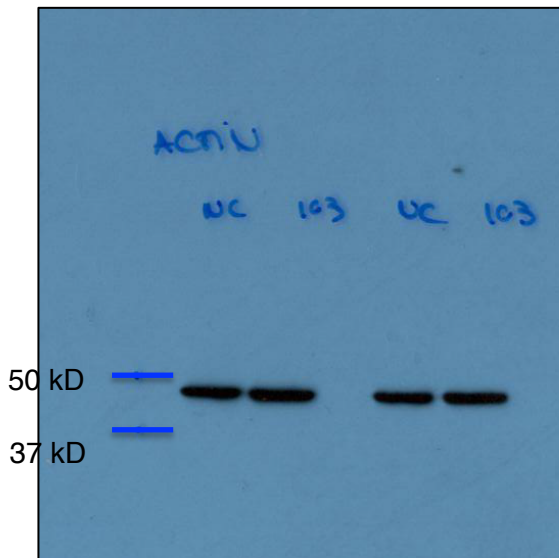
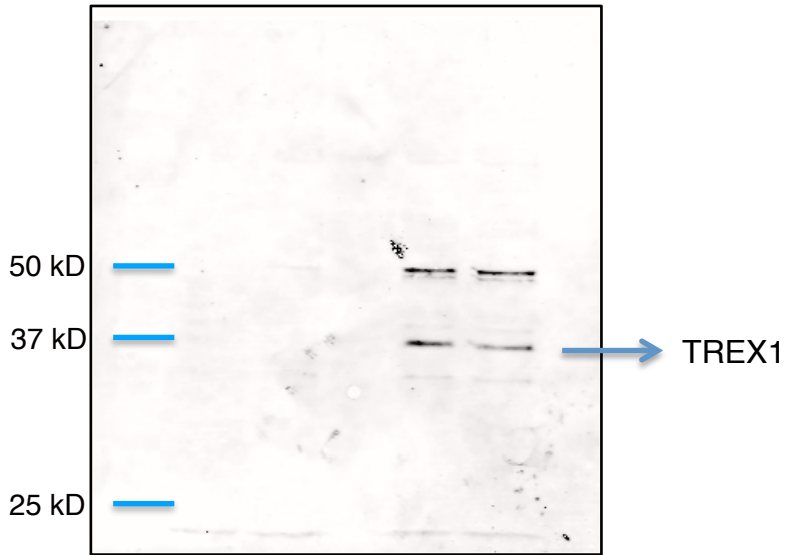
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### Supplementary Figure 10. RNA hybrid models of miR-103 binding sites

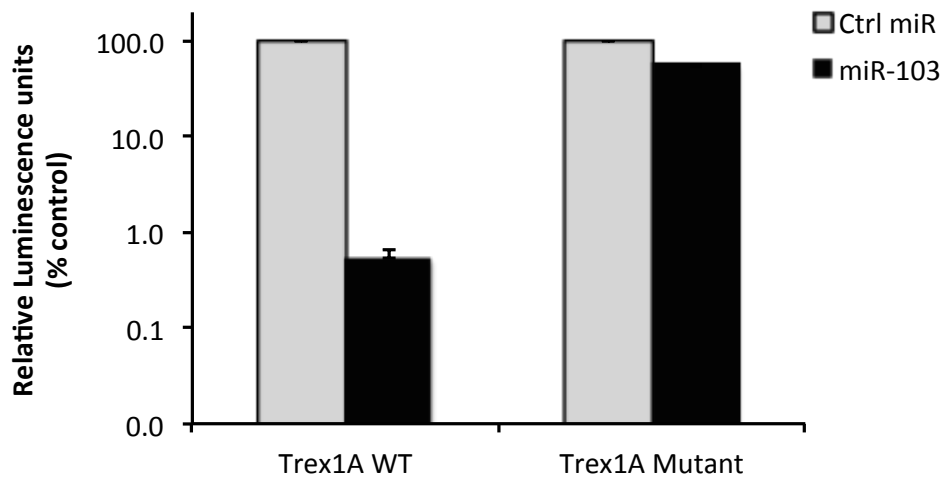
(A) mRNA sequence of human TREX1 showing miR-103 binding sites in the coding region. (B) RNA hybrid modeling of the miR-103 TREX1 interaction reveals high binding energies for the two sites. (C) mRNA sequence of human FANCF showing the stop codon and miR-103 binding site. (D) RNA hybrid modeling of the miR-103-FANCF interaction. miR binding sites are conserved between human and mouse TREX1 and FANCF.

Ctrl miR-103

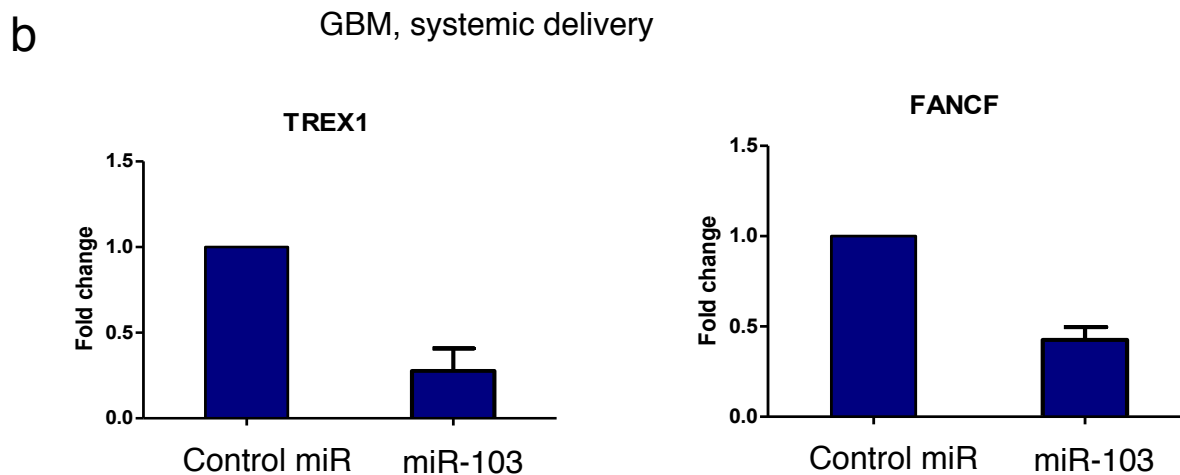
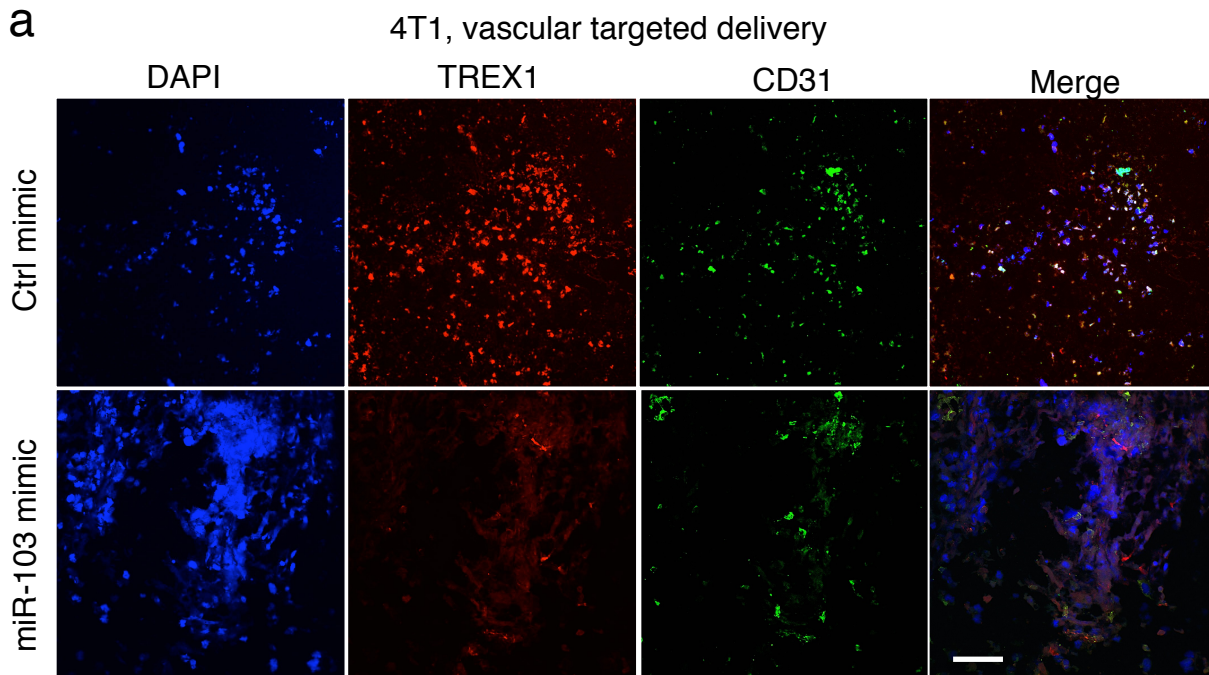


Supplementary Figure 11. Full lane images of western blots from figure 3

TREX 1 A	ctg <b>gagccctatccagggaggggctgctg</b> gcc
TREX 1 A Mut	ctg <b>gag</b> <b>aaa</b> <b>at</b> <b>ccagggaggg</b> <b>aaataa</b> <b>g</b> gcc



**Supplementary Figure 12. TREX1 A site harbors a specific binding region for miR-103.** Top panel shows the binding region of miR-103 on TREX1 coding region (green shaded) and the mutations (grey shaded). Luminescence from 3'UTR-luciferase constructs with either WT or mutant miR-103 binding regions 24h after transfection with Control miR or miR-103. Bars show mean + SEM.

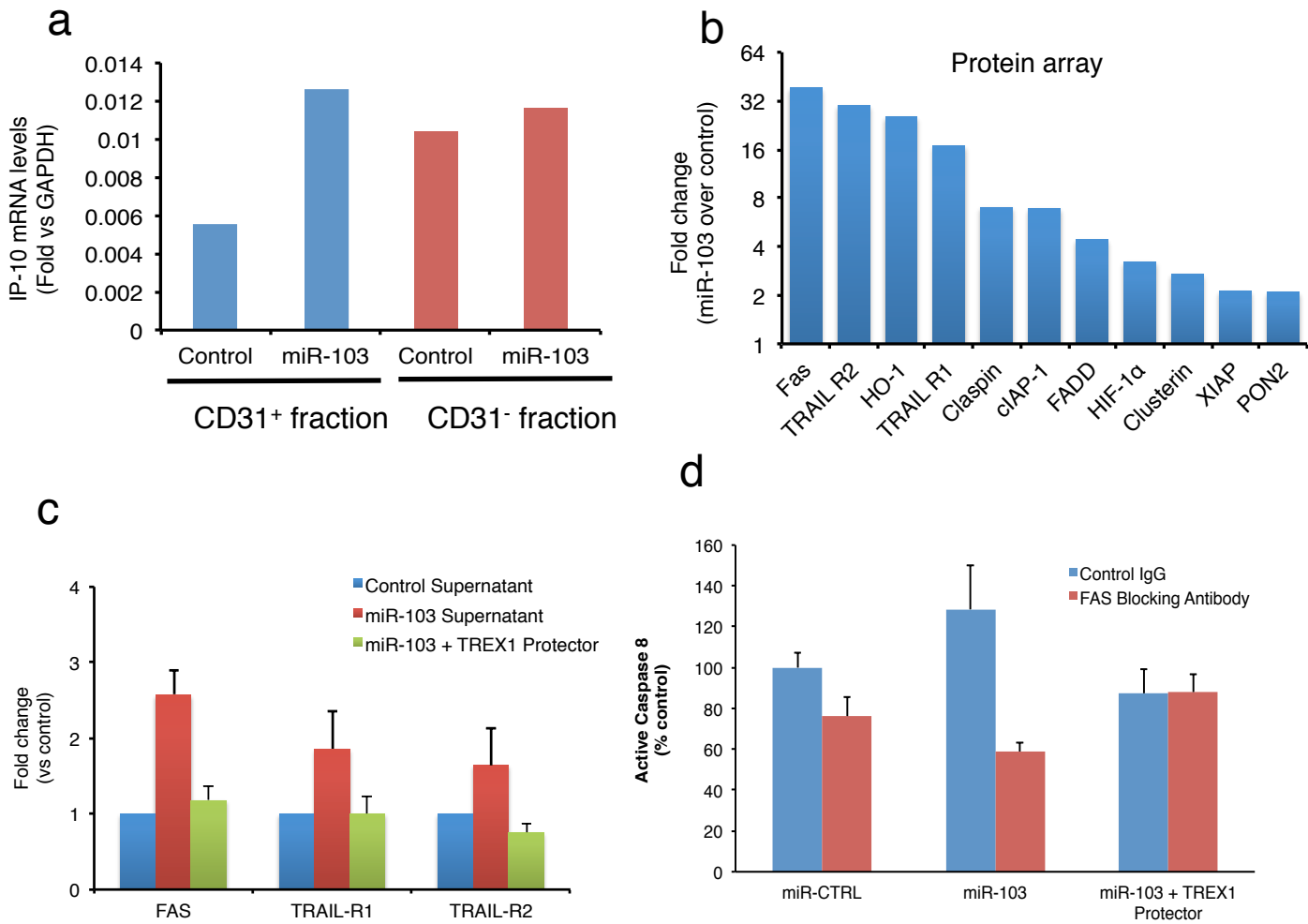


**Supplementary Figure 13. miR-103 treatment decreases endothelial TREX1 in vivo.** **a)** Representative Immunofluorescence images from sections stained for TREX1 and CD31 from 4T1 tumors treated with either miR mimic or miR-103 in 7C1 nanoparticles (Fig 3 f-g). Scale bar = 100  $\mu$ m. **b)** Nu/Nu mice were injected with GBM-NS-001 cells ( $1 \times 10^6$  cells) subcutaneously. 20 days post injection, the mice were randomized to miR control or miR103 (n=5 per group and 15 nanomoles of miR was injected i.v. Tumors were harvested 48h later and endothelial cells were sorted as CD45-CD31+CD34+ followed by RT-PCR analysis. Bars show mean + SEM.

	24h		48h		72h	
	miR-103	miR-103+TREX1 Protector	miR-103	miR-103+TREX1 Protector	miR-103	miR-103+TREX1 Protector
IP-10	38.9	1.5	60.6	1.0	53.9	0.6
RANTES	13.5	3.9	74.5	2.3	63.9	0.8
IL-15	8.3	1.0	8.3	2.5	4.5	1.0
MIG	7.0	7.0	1.0	0.1	7.0	1.0
MIP-1alpha	3.4	2.2	2.2	2.2	1.6	1.0
IL-12	2.7	0.0	1.0	0.0	7.4	0.0
INF-gamma	2.4	2.4	2.4	0.5	3.3	0.7
IL-13	1.9	0.0	49.8	49.8	0.0	0.0
MCP-1	1.5	0.2	1.6	0.1	1.0	0.0
IL-2	1.4	1.2	1.2	1.0	1.4	1.0
IL-6	1.3	2.2	0.8	0.6	0.5	0.1
MIP-1beta	1.3	1.0	1.0	1.0	1.3	1.0
IL-4	1.2	1.0	0.8	1.0	1.0	0.7
IL-1RA	1.2	0.9	1.0	1.1	1.1	1.0
IL-17	1.2	1.2	0.9	0.9	1.2	1.0
IL-10	1.0	0.9	1.0	1.0	1.0	1.0
GM-CSF	1.0	0.9	0.9	0.9	0.7	0.7
INF-alpha	1.0	1.0	1.0	1.0	1.0	0.1
TNF-alpha	1.0	2.0	3.3	1.0	2.0	1.0
IL-7	1.0	1.0	3.4	0.8	33.1	1.0
IL-2R	1.0	1.5	1.5	1.0	1.0	1.0
IL-5	0.9	0.9	1.0	1.0	0.9	1.0
Eotaxin	0.9	1.5	1.2	0.8	1.0	1.0
IL-1Beta	0.5	0.5	0.5	1.0	1.0	1.0
IL-8	0.4	0.2	0.4	0.1	0.1	0.0

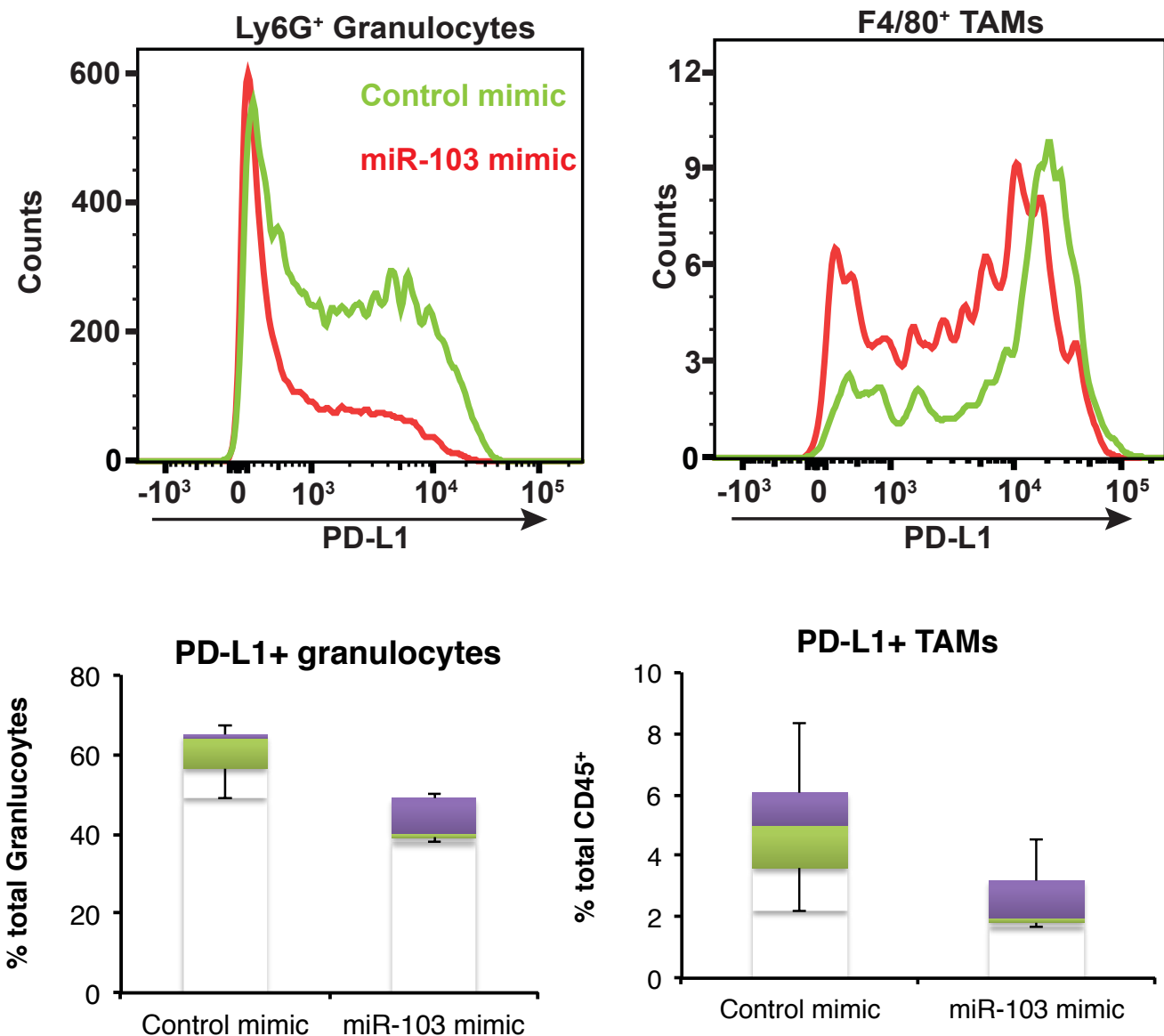
**Supplementary Figure 14. Secretome induced by miR-103 expression.**

HUVECs were transfected with miR-103 or a control miR and supernatant was harvested at the indicated time points. The supernatants were analyzed for cytokine expression using a human cytokine/chemokine multiplex luminex assay. Heatmap depicts fold change in miR-103 treated supernatants with or without TREX1 target protectors vs control miR supernatants.



**Supplementary Figure 15. miR-103 causes tumor cell death in a paracrine fashion.**

(a) Upregulation of IP10 mRNA in tumor endothelial cells after 7C1 delivery of miR-103 in HCT116 xenografts. Day 17 tumors from Fig 3c were used for this assay. (b) Protein expression on a cell survival membrane array using whole tumor lysate of a HCT116 tumor 48h after a single miR-103 injection compared to control miR injection. (c) Gene expression in HCT116 cells after 72h of culture with conditioned media from HUVECs transfected with either Control miR, miR-103 or miR-103+TREX1 target protector. Bars depict mean + SD fold change. (d) Active Caspase-8 levels of HCT116 cells 72h after treatment with conditioned media from HUVECs transfected with the indicated oligos. Bars depict mean + SD % change over control miR transfected, control IgG treated cells.



**Supplementary Figure 16. miR-103 treatment affects the immune microenvironment** Representative flow cytometry histogram plots and box plots of PD-L1 expression on Ly6G<sup>+</sup> granulocyte population and F4/80<sup>+</sup> tumor associated macrophages from 4T1 tumor bearing mice treated with either control mimic or miR-103 mimic as described in Fig 3f. (n=3 mice per group). Bars show interquartile range.