Samples sizes are described in the Figure Legends.

Specifically, sample sizes for each data set are as follows. Fig. 1a: n = 3 biological replicates. Fig. 1b: n = 6 (3 biological replicates, 2 technical replicates per mouse). Fig. 1c: n = 10 (2 biological replicates, 5 fields of view per bone). Fig. 1e-j: n = 11 (Oil ERα-KO, 6 recipients per donor), n = 18 (E2-ERαKO, 6 recipients per donor), n = 24 (Oil and E2 WT, 6 recipients per donor). Fig. 2a-c: n = 4 biological replicates. Fig. 2d-f: n = 4 (Oil WT, Oil ERα-KO, E2 ERα-KO), n = 5 (E2 WT). Fig. 2g: n = 7 (E2), n = 9 (Oil). Fig. 2h: n = 9 (Female), n = 10 (Male). Fig. 3a-c: n = 4 (Oil and E2 Day 3,5, and 14), n = 6 (Oil and E2 Day 7). Fig. 3d: n = 5 (Unirradiated, 1 donor), n = 7 (Oil, 4 recipients per donor), n = 8 (E2, 4 recipients per donor). Fig. 3e-g: n = 3 (E2 Unirradiated), n = 4 (Oil ERα-KO TBI), n = 5 (E2 ERα-KO TBI), n = 6 (Oil Unirradiated, E2 TBI), n = 7 (Oil TBI). Fig. 4a: n = 8 (2 biological replicates per group). Fig. 4e: n = 3 biological replicates. Fig. 4f: n = 3 biological replicates. Fig. 4g: n = 3 biological replicates. Fig. 5a: n = 5 biological replicates. Fig. 5b: n = 4 (E2), n = 5 (Oil). Fig. 5d: n = 3 (E2 Unirradiated, E2 TBI), n = 4 (Oil TBI), n = 5 (Oil Unirradiated). Fig. 5f: n = 3 biological replicates. Fig. 5g: n = 7 (sgRNA-Ire1 E2), n = 9 (sgRNA-Rosa26 Oil and E2), n = 10 (sgRNA-Ire1 Oil). Fig. S1c: n = 8 (E2, 4 recipients per donor), n = 11 (Oil, 4 recipients per donor). Fig. S2a-d: n = 4 (Oil Unirradiated), n = 5 (Oil and E2 TBI). Fig. S2e-f: n = 4 (Oil and E2 Day 3,5, and 14), n = 6 (Oil and E2 Day 7). Fig. S2g: n = 3 (E2 Unirradiated), n = 4 (Oil ERα-KO TBI), n = 5 (E2 ERα-KO TBI), n = 6 (Oil Unirradiated, E2 TBI), n = 7 (Oil TBI). Fig. S2h: n = 3 (Unirradiated control), n = 4 (Oil and E2 TBI Days 3 and 5). Fig. S3a: n = 3 biological replicates. Fig. S4a: n = 3 biological replicates. Fig. S4b: n = 3 biological replicates. Fig. S4c: n = 3 biological replicates. Fig. S4d: n = 3 biological replicates. Fig. S4e: n = 4 biological replicates. Fig. S4f: n = 3 (G-CSF), n = 4 (Poly(I:C)). Fig. S5: n = 3 biological replicates.

Statistical reporting

- Statistical analysis methods should be described and justified
- Raw data should be presented in figures whenever informative to do so (typically when N per group is less than 10)
- For each experiment, you should identify the statistical tests used, exact values of N, definitions of center, methods of multiple test correction, and dispersion and precision measures (e.g., mean, median, SD, SEM, confidence intervals; and, for the major substantive results, a measure of effect size (e.g., Pearson's r, Cohen's d)
- Report exact p-values wherever possible alongside the summary statistics and 95% confidence intervals. These should be reported for all key questions and not only when the p-value is less than 0.05.

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn't apply to your submission:

Statistical analysis methods are described in each figure legends, as well as in the "Quantification and Statistical Analysis" section of the Materials and Methods. Specifically, unless indicated otherwise in the figure legends, analyses were always carried out in comparison to the control group (Oil, DMSO, etc). When comparing means from groups with unequal sample sizes, Mann Whitney tests were used for the comparison of two groups (Fig S5d), and Kruskal Wallis tests with Dunn's multiple comparison tests were used for comparing three or more groups (Fig 6e). Otherwise, two-tailed t-tests were used for the comparison of two groups (Fig. 1c, 2a-c, 3a-d, 5a, and Supplementary Fig S2f-g, i, S3a, S4b,f) and one- and two-way ANOVAs for comparisons involving more than two groups or more than two independent variables (Figs 1a-b, e-j, 2d-f, 3d-g, 4d-g, 5d-e, 6b,d and Supplementary Fig S1d, S2b-e, h, S3b-i, S4c-g, S5c-d) with Bonferroni corrections performed for multiple testing. Analysis of survival curves was performed using a log-rank test (Fig 2g-h).

(For large datasets, or papers with a very large number of statistical tests, you may upload a single table file with tests, Ns, etc., with reference to sections in the manuscript.)

Group allocation

- Indicate how samples were allocated into experimental groups (in the case of clinical studies, please specify allocation to treatment method); if randomization was used, please also state if restricted randomization was applied
- Indicate if masking was used during group allocation, data collection and/or data analysis

Please outline where this information can be found within the submission (e.g., sections or figure legends), or explain why this information doesn't apply to your submission:

This is described in the "Quantification and Statistical Analysis" section of Materials and Methods. All mice were age and sex matched for each experiment. Unless indicated otherwise only male mice were used, and littermate controls were used for ERaKO studies. Distribution of mice was not formally randomized, and no experiments were blinded.

Additional data files ("source data")

- We encourage you to upload relevant additional data files, such as numerical data that are represented as a graph in a figure, or as a summary table
- Where provided, these should be in the most useful format, and they can be uploaded as "Source data" files linked to a main figure or table
- Include model definition files including the full list of parameters used
- Include code used for data analysis (e.g., R, MatLab)
- Avoid stating that data files are "available upon request"

Please indicate the figures or tables for which source data files have been provided:

No source data files are provided.