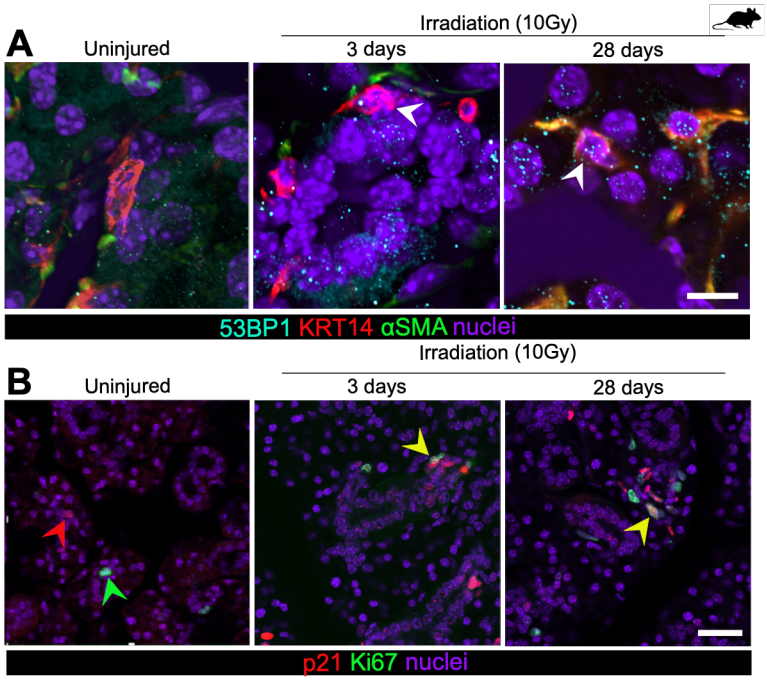

Figure S1

A. Representative expression of Keratin-14 (KRT14), αSMA, 53BP1 and nuclei in the SMG of uninjured mice or mice irradiated 3 or 28 days earlier. White arrows indicate cell with DNA damage foci. Scale bar = 20μm.

B. Representative expression of p21, Ki67 and nuclei in the SMG of uninjured mice or mice irradiated 3 or 28 days earlier. Red arrows denote $p21^+$ cells, green arrows denote $Ki67^+$ positive cells, yellow arrows denote $p21^+$ $Ki67^+$ dual positive cells. Scale bar = 50μm.

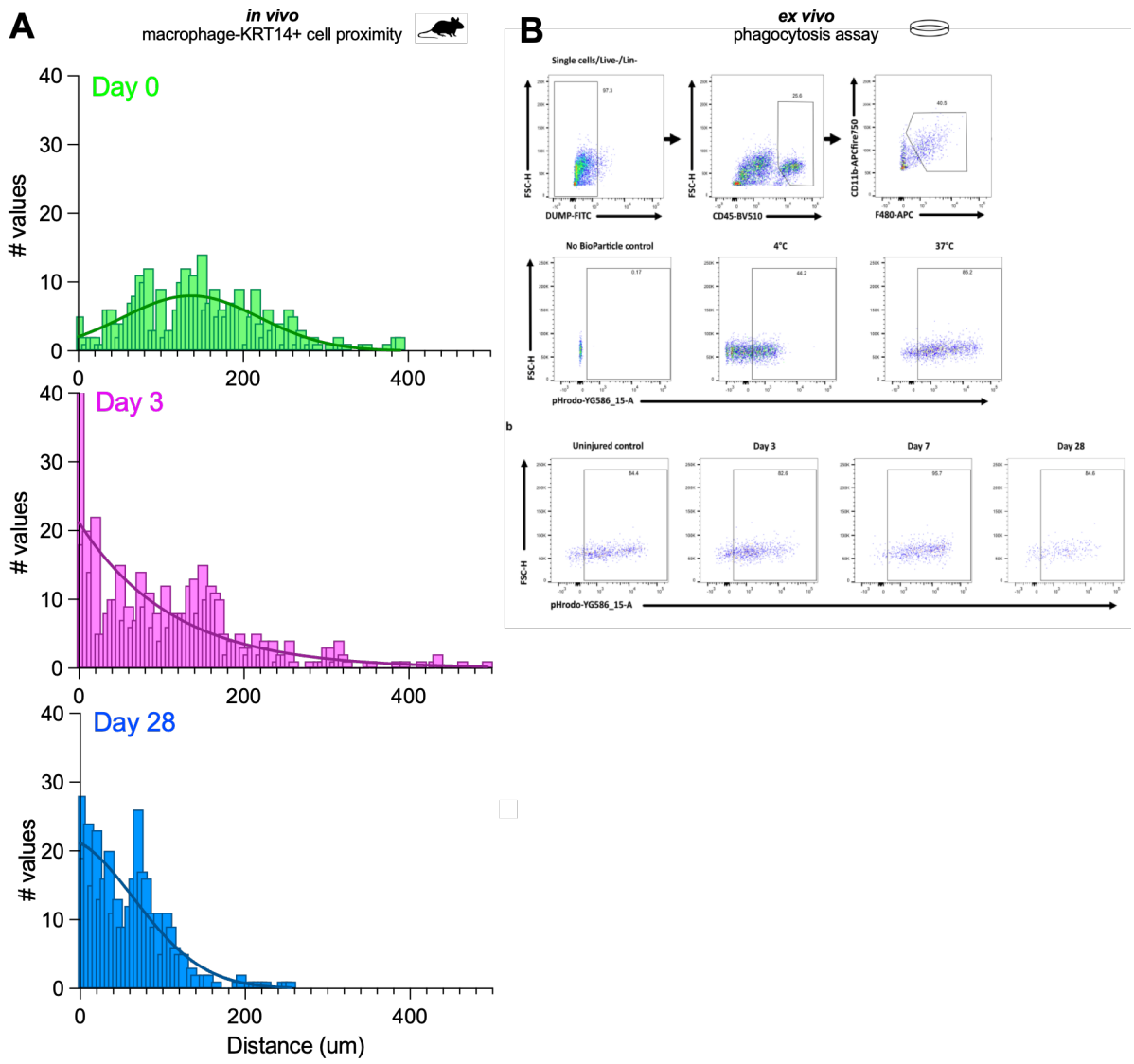

Figure S2

A. Graphs showing the distance between F4/80^{+} macrophages and KRT14+ basal epithelia progenitor cells, in the SMG of uninjured mice or mice irradiated 3 or 28 days earlier, measured using nearest neighbour analysis. Data obtained from three fields of view from non-sequential sections from 3 mice per timepoint. Merged graph is shown in **Figure 1I**.

B. Representative expression of pHrodo-YG586 by SiglecF^{-}Ly6G^{-}CD45^{+}F4/80^{+}CD11b^{+} cells obtained from SMG of uninjured mice or mice which have been exposed to 10Gy irradiation 3, 7 or 28 days previously, and incubated with pHrodo beads for 1 hour at either 4 °C or 37 °C.

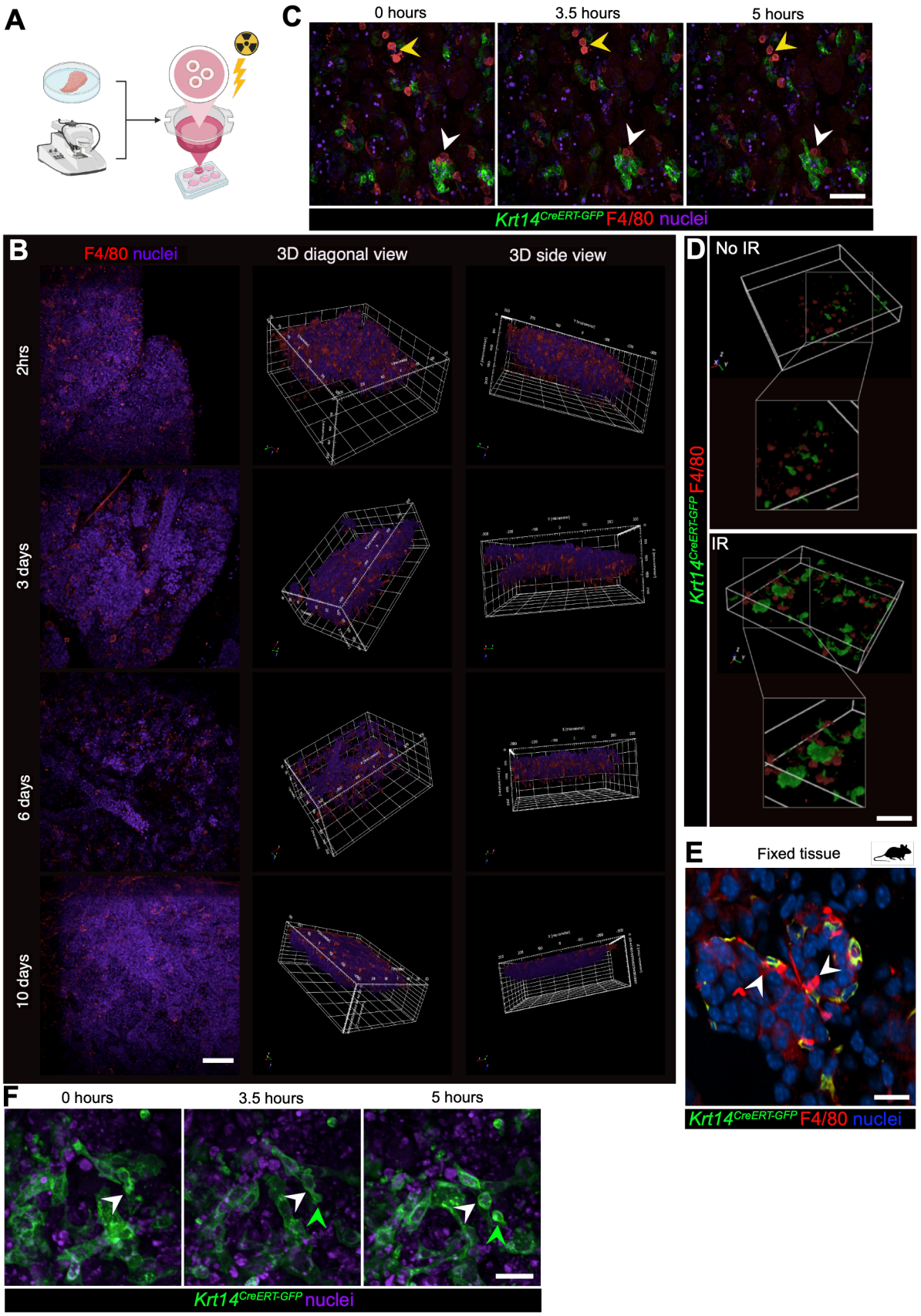

Figure S3

A. Experimental scheme of the organotypic slice culture system coupled with irradiation.

B. Representative expression of F4/80 and nuclei in the organotypic slices of SMG following 10 Gy irradiation, analysed after 2 hours or 3, 6, or 10 days of culture. Scale bar = 100μm. Middle and right panels show 3D images acquired from 150 μM z-stacks showing F4/80 expression within SMG slices from diagonal (middle) and side (right) views. Magnification 20x.

C. Representative still images from live cell imaging of *Krt14*$^{CreERT\text{-}GFP}$ cells, F4/80^{+} macrophages and nuclei after 0, 3.5 and 5 hours in culture. Scale bar = 200μm.

D. Computer generated rendering to display cell-cell contact between *Krt14*$^{CreERT\text{-}GFP+}$ cells and F4/80^{+} macrophages, after 1 day in culture, with and without exposure to 10Gy irradiation (IR). Scale bar = 200μm.

E. Representative expression of *Krt14*$^{CreERT\text{-}GFP}$ cells and F4/80^{+} macrophages in the SMG of uninjured mice. White arrows denote intraepithelial macrophages. Scale bar = 20μm.

F. Representative still images from live cell imaging of *Krt14*$^{CreERT\text{-}GFP}$ cells and nuclei after 0, 3.5 and 5 hours in culture. Scale bar = 100μm. White arrows show *Krt14*$^{CreERT\text{-}GFP}$ cell undergoing division over 5 hours of live imaging; green arrows indicates daughter cell. z-stacks were taken at 20x magnification every 15 minutes.

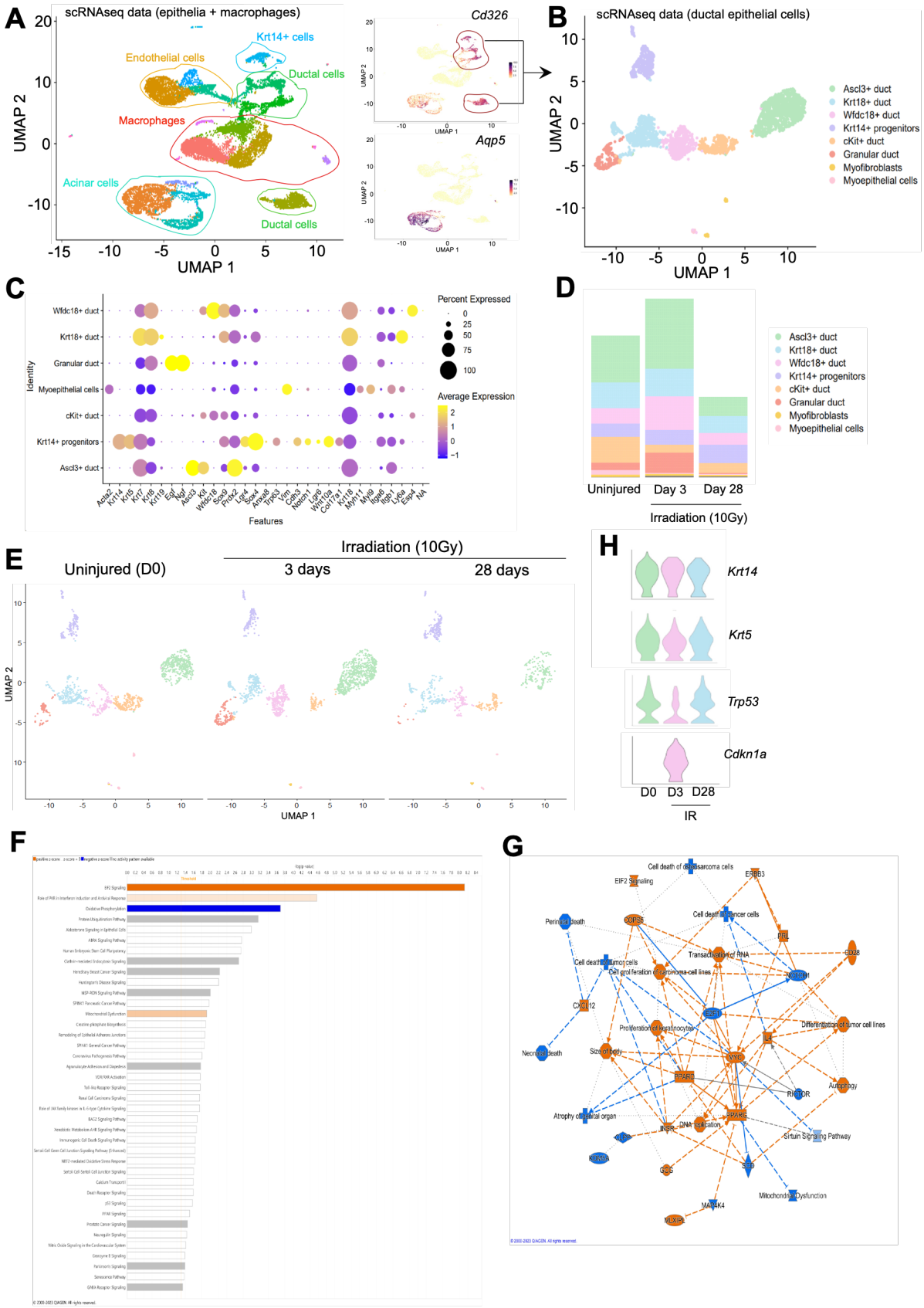
A
scRNAseq data (epithelia + macrophages)
Krt14+ cells
Endothelial cells
Ductal cells
Macrophages
Acinar cells
Ductal cells
UMAP 1
UMAP 2
Cd326
Aqp5
B
scRNAseq data (ductal epithelial cells)
Ascl3+ duct
Krt18+ duct
Wfdc18+ duct
Krt14+ progenitors
cKit+ duct
Granular duct
Myofibroblasts
Myoepithelial cells
C
Wfdc18+ duct
Krt18+ duct
Granular duct
Myoepithelial cells
cKit+ duct
Krt14+ progenitors
Ascl3+ duct
Identity
Features
Percent Expressed
Average Expression
D
Uninjured
Day 3
Day 28
Irradiation (10Gy)
E
Uninjured (D0)
Irradiation (10Gy)
3 days
28 days
H
Krt14
Krt5
Trp53
Cdkn1a
D0 D3 D28
IR
F
G
Cell death of osteosarcoma cells
EIF2 Signaling
ERBB3
Cell death of cancer cells
Perinatal death
CDKN2A
Transactivation of RNA
Cell death of tumor cells
Cell proliferation of carcinoma cell lines
CXCL12
Proliferation of keratinocytes
Differentiation of tumor cell lines
Neonatal death
Size of body
PPARG
RICTOR
Autophagy
Atrophy of skeletal muscle
DNA methylation
Sirtuin Signaling Pathway
Mitochondrial Dysfunction
MAP4K4

Figure S4

A. UMAP dimensionality reduction analysis of scRNA-seq data from SMG epithelial cells and macrophages. Insets of feature plots showing expression of *Cd326* and *Aqp5* to discern between ductal and acinar cells, respectively.

B. UMAP dimensionality reduction analysis of scRNA-seq data from SMG ductal epithelial (*Cd326*$^{+}$) cells, annotated by gene expression.

C. Bubble plot showing expression of selected conserved genes by ductal epithelial clusters between the SMG of uninjured mice or mice irradiated 3 or 28 days earlier.

D. Absolute number of each ductal epithelial cell sub-cluster defined in **Figure S4B** from SMG of uninjured mice or mice irradiated 3 or 28 days earlier.

E. UMAP dimensionality reduction analysis of scRNA-seq data of *Cd326*$^{+}$ ductal cells from SMG of uninjured mice or mice irradiated 3 or 28 days earlier, and split by timepoint.

F. Qiagen Ingenuity Pathway Analysis of top differentially expressed pathways in all ductal clusters identified in **Figure S4B** at day 3 post-IR vs uninjured control. Orange bars represent activated and blue inactivated pathways.

G. Qiagen Ingenuity Pathway Analysis showing summary of signalling pathways and gene interactions in the *Krt14*$^{+}$ progenitor cell cluster in day 3 irradiated vs non-irradiated mice. Orange represents predicted activation, blue represents predicted inhibition. Solid lines represent direct interactions, largely spaced dashed lines indirect interactions, small spaced dashed lines inferred relationships.

H. Violin plots showing expression of *Krt14, Krt5, Trp53 and Cdkn1a* in *Cd326*$^{+}$ ductal cells from SMG of uninjured mice or mice irradiated 3 or 28 days earlier, and split by timepoint.

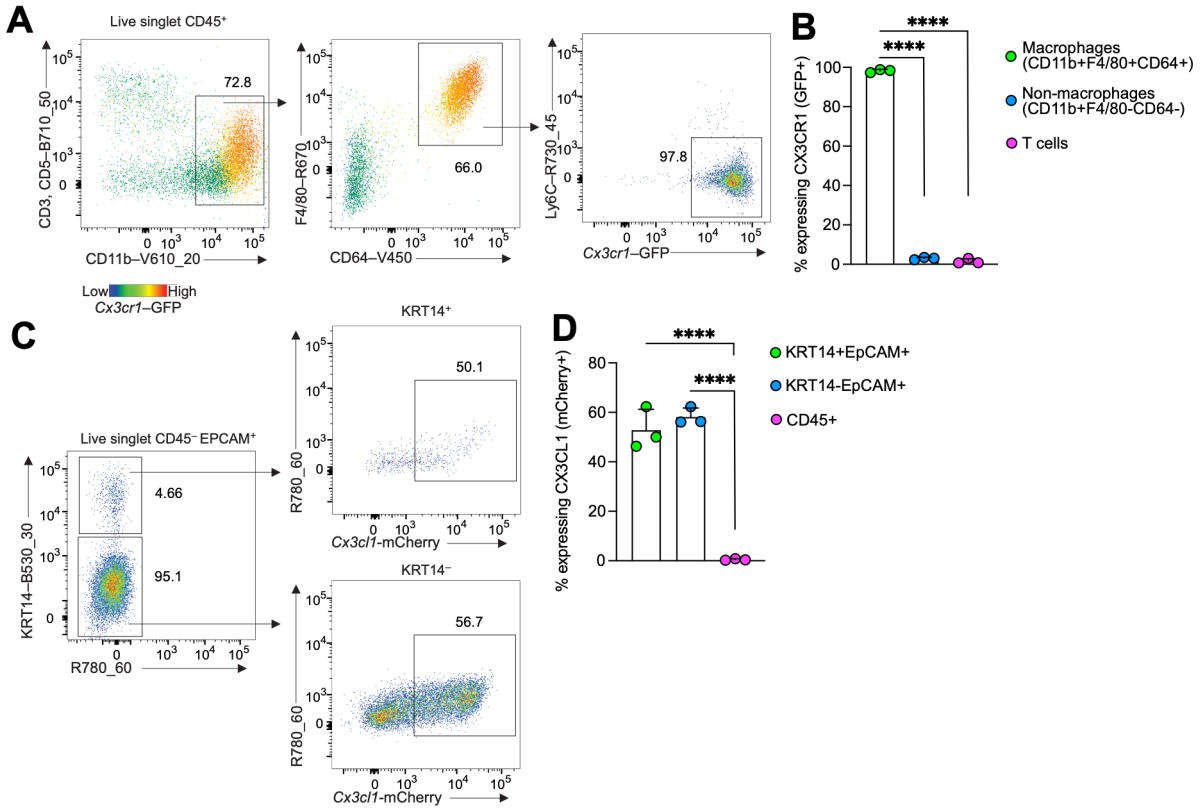

Figure S5

A. Representative gating strategy (CD3–CD5–CD11b^{+}CD64^{+}F/4/80^{+}Ly6C– cells) for analysis of *Cx3cr1*-GFP^{+} cells from SMG of *Cx3cr1*^{GFP}*; Cx3cl1*^{mCherry} mice.

B. Graphical enumeration of percentage of cells expressing CX3CR1 (GFP^{+}). Data are from 3 mice. ****p<0.0001 (One-way ANOVA followed by Tukey Q post-hoc testing). Symbols represent individual mice and error bars represent the SD.

C. Representative gating strategy (CD45–EpCAM^{+} cells) for analysis of KRT14^{+} and KRT14– cells for *Cx3cl1*^{mCherry} in SMG from *Cx3cr1*^{GFP}*; Cx3cl1*^{mCherry} mice. R780_60 is an empty channel.

D. Graphical enumeration of percentage of cells expressing CX3CL1 (mCherry^{+}). Data are from 3 mice. ****p<0.0001 (One-way ANOVA followed by Tukey Q post-hoc testing). Symbols represent individual mice and error bars represent the SD.

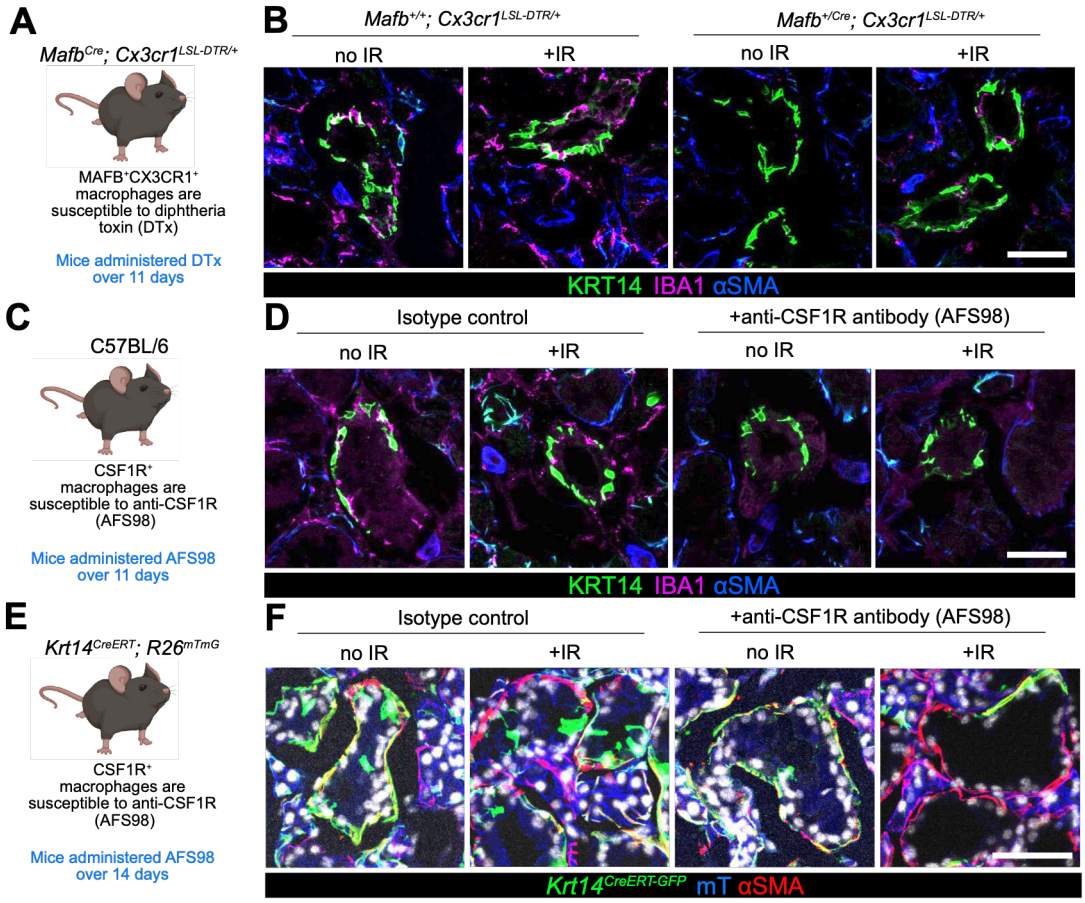

Figure S6

A. Experimental scheme for macrophage depletion in *Mafb*$^{Cre/+}$.*Cx3cr1*$^{LSL\text{-}DTR/+}$ mice.

B. Representative immunofluorescent images of SMG stained for KRT14, IBA and αSMA in *Mafb*$^{Cre/+}$.*Cx3cr1*$^{LSL\text{-}DTR/+}$ or *Mafb*$^{+/+}$.*Cx3cr1*$^{LSL\text{-}DTR/+}$ littermates exposed to 0Gy or 10Gy irradiation and administered diphtheria toxin (DTx) or saline from day 17 onwards, every 2 days and analysed 28 days after irradiation. Scale bar = 50μm.

C. Experimental scheme for macrophage depletion in C57BL/6 mice using anti-CSF1R antibody AFS98.

D. Representative immunofluorescent images of SMG stained for KRT14, IBA and αSMA in C57BL/6 mice exposed to 0Gy or 10Gy irradiation before being administered anti-CSF1R (AFS98) or isotype control and analysed 28 days after irradiation. Scale bar = 50μm.

E. Experimental scheme for lineage tracing and macrophage depletion experiments using *Krt14*^{CreERT}; *R26*^{mTmG} mice and anti-CSF1R antibody AFS98.

F. Representative immunofluorescent images of SMG stained for KRT14, IBA and αSMA in C57BL/6 mice exposed to 0Gy or 10Gy irradiation before being administered anti-CSF1R (AFS98) or isotype control and analysed 28 days after irradiation. Scale bar = 50μm.

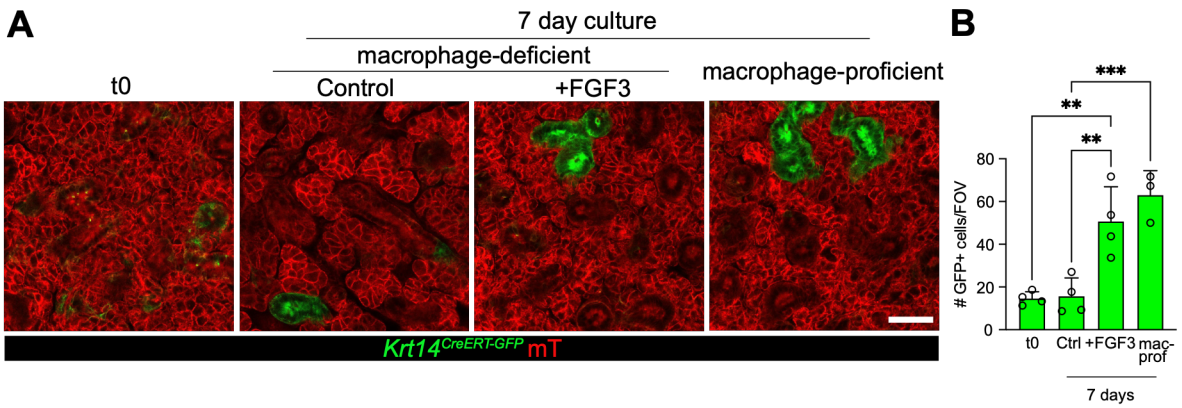

Figure S7

A. Representative immunofluorescent images of organotypic SMG slices from macrophage-deficient or macrophage-proficient *Krt14^{CreERT}; R26^{mTmG}* mice at time zero (t0), or cultured for 7 days with and without exogenous FGF3. Scale bar = 50μm.

B. Graphical enumeration *Krt14$^{CreERT-GFP+}$* cells in SMG slices at time zero (t0), or following culture for 7 days with and without exogenous FGF3. Data obtained from three fields of view per slice, from 3 slices per condition, from 3-4 mice, over 2 independent experiments. **p<0.01, ***p<0.001.