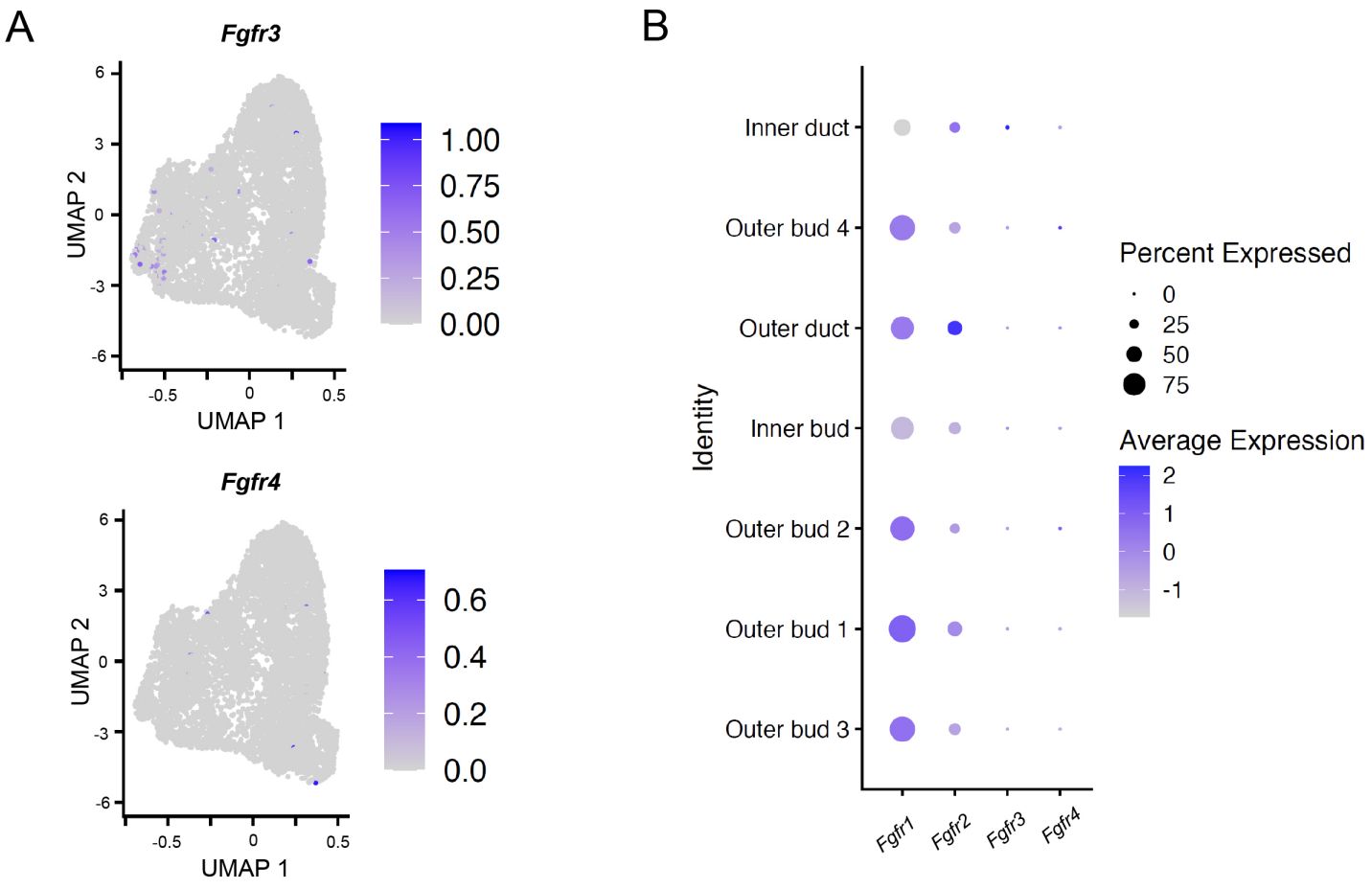


Fig. S1 (related to Fig. 1).

(A) Scatterplot of scRNA-Seq data, GSE159780, (Wang et al., 2017) for SMG epithelial cells at E13 was reanalyzed. UMAP embedding followed by color coding was used to analyze expression of *Fgfr3* and *Fgfr4*. Each dot represents a single cell.

(B) Dot plot showing the relative expression of FGFRs (*Fgfr1*, *Fgfr2*, *Fgfr3* and *Fgfr4*) in each cluster.

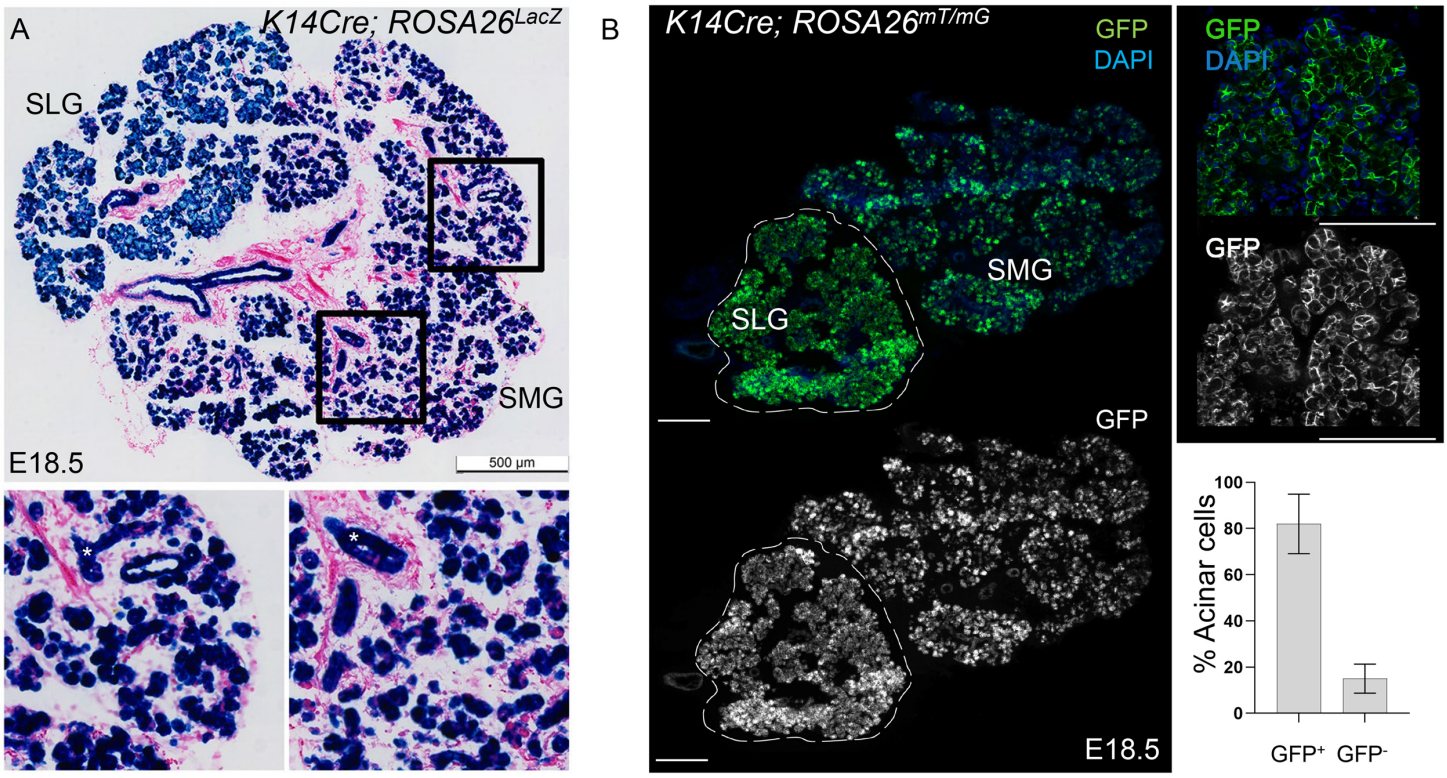


Fig. S2 (related to Fig. 2).

(A) *K14cre* mice were crossed to *ROSA26*^{LacZ} reporter mice to investigate the contribution of *K14*-lineage to the developing salivary gland at E18.5. LacZ reporter activity was restricted to the epithelial compartment. Stromal cells did not show reporter activity. Epithelial cells of the acini were labeled in both the SMG and SLG. Cells in the inner lining of developing epithelial tubes were also labeled (white asterisks).

(B) *K14Cre* mice were crossed to *ROSA26*$^{mT/mG}$ reporter mice to further validate the *K14*-lineage contribution in the salivary gland. The bar graph shows that 85% of the cells in the SMG express GFP.

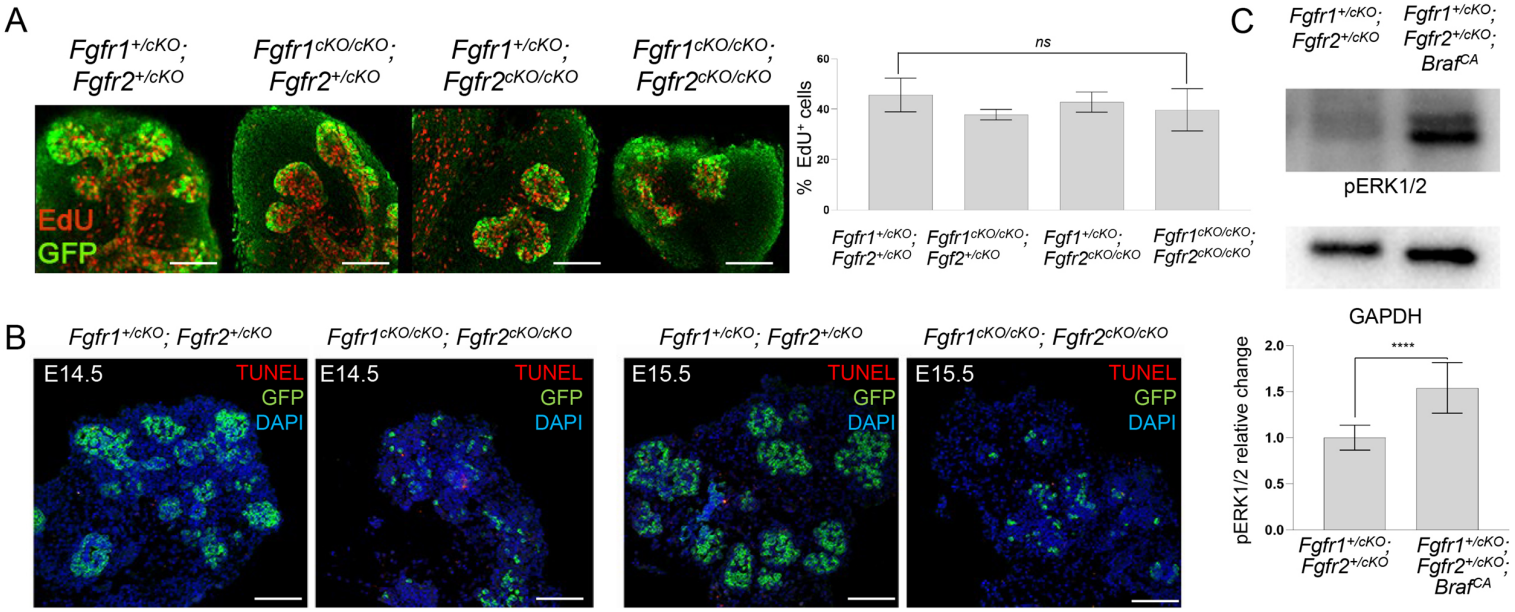


Fig. S3 (related to Fig. 3).

(A) EdU incorporation (red) was used to assess the extent of cell proliferation across *Fgfr1/2; ROSA26*^{mTmG} conditional mutants (*n=3*, *Fgfr1*$^{cKO/cKO}$*; Fgfr2*$^{cKO/cKO}$*; ROSA26*^{mTmG} compound mutants, *n=12 Fgfr1*$^{cKO+}$*; Fgfr2*$^{cKO/+}$*; ROSA26*^{mTmG}) at E14.5. SMG *K14Cre* lineage^{+} cells expressed GFP (Green). Significant levels of EdU incorporation, both in the stromal cells as well as within the GFP^{+} domain, were detected across all *Fgfr1/2* compound mutants. Results were quantified for each *Fgfr1/2* mutants analyzed and represented in a bar graph.

(B) TUNEL was used to assess the extent of cell death in SMG in *Fgfr1*$^{+/cKO}$*; Fgfr2*$^{+/cKO}$*; ROSA26*^{mTmG} control (*n=4*) and *Fgfr1*$^{cKO/cKO}$*; Fgfr2*$^{cKO/cKO}$*; ROSA26*^{mTmG} compound mutants (*n=5*) at E14.5 (left) and E15.5 on sections (right). A few apoptotic cells were detected which were restricted to the stromal cells in controls and mutants. Very few epithelial specific TUNEL positive foci could be detected. Scale bars, 100 μm.

(C) Western blot shows phosphorylated ERK1/2 levels in freshly harvested salivary glands *Fgfr1*$^{+/cKO}$; *Fgfr2*$^{+/cKO}$*; Braf*^{CA} mutants (*n=3*) and control *Fgfr1*$^{+/cKO}$; *Fgfr2*$^{+/cKO}$ compound heterozygotes (*n=4*). The levels were quantified by western blot and represented in a bar graph.

Data expressed as mean (+/-SD), * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001, ns P<0.05 (One-way ANOVA using Bonferroni multiple comparisons test, two-tailed, or Student's T-test, two-tailed).

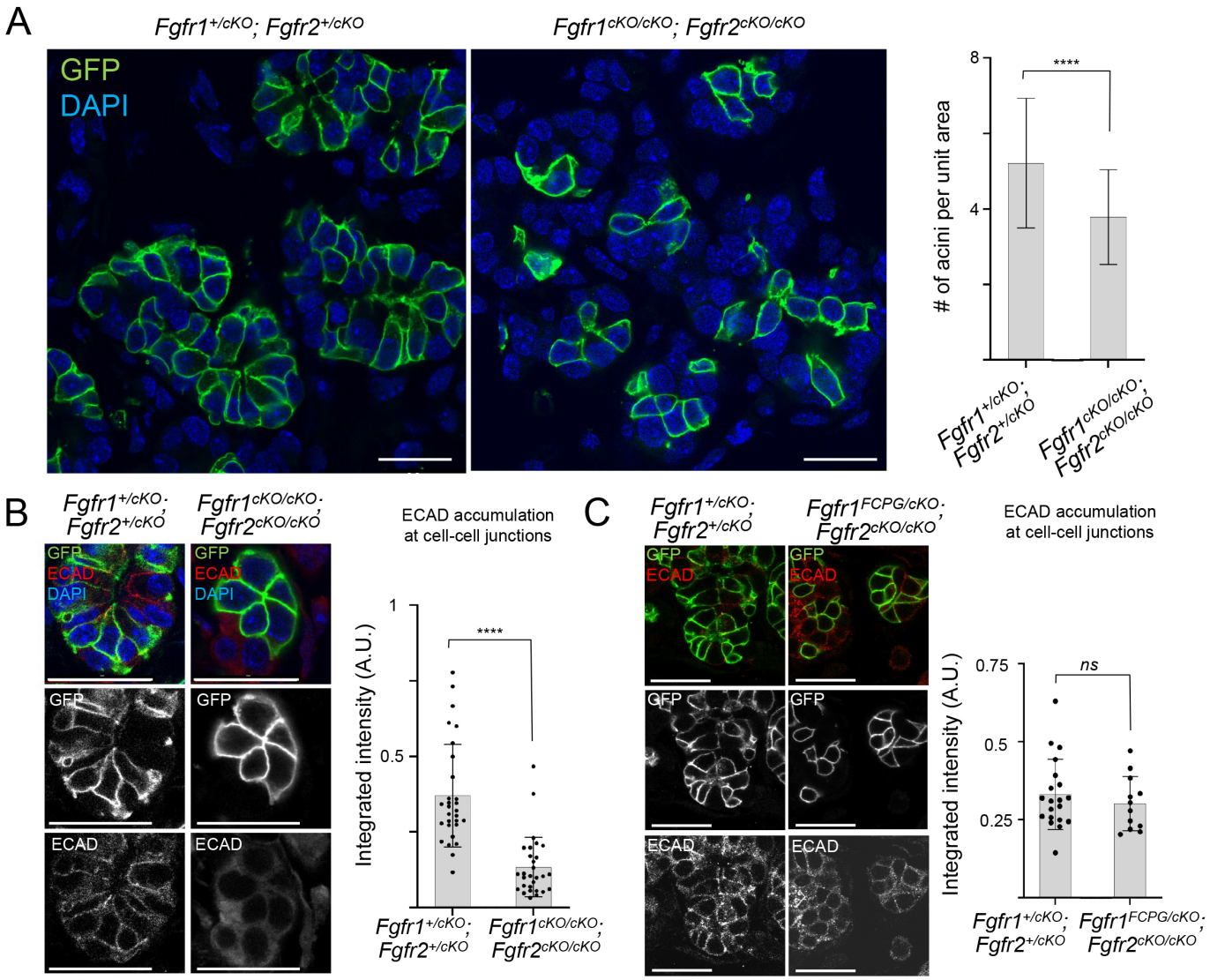


Fig. S4 (related to Fig. 4).

(A) SMGs were analyzed at E15.5 on sections. Multiple GFP⁺ cells in control *Fgfr1*$^{+/cKO}$*; Fgfr2*$^{+/cKO}$ mutants (*n=3*) made robust cell-cell contacts in the acini. GFP⁺ cells in *Fgfr1*$^{cKO/cKO}$*; Fgfr2*$^{cKO/cKO}$ compound mutants (*n=4)* were found less frequently and accordingly showed fewer cell-cell contacts. *Fgfr1*$^{cKO/cKO}$*; Fgfr2*$^{cKO/cKO}$ compound mutants also developed fewer acini. The bar graph represents the number of number of acini in control *Fgfr1*$^{+/cKO}$*; Fgfr2*$^{+/cKO}$ versus *Fgfr1*$^{cKO/cKO}$*; Fgfr2*$^{cKO/cKO}$ compound mutants. Scale bars, 20 μm.

(B) E-cadherin expression levels was analyzed in the GFP$^+$ *K14-Cre* lineage cells at cell-cell junctions for control and compound *Fgfr1/2* mutants at E15.5. Robust ECAD expression between GFP$^+$ *K14 Cre* lineage were observed in controls. Cell-cell boundaries in *Fgfr1/2* compound null mutants showed low E-cadherin levels. Integrated intensities were measured for ECAD in *Fgfr1/2* compound *null* mutants and controls and their normalized means are plotted as a bar graph. A large reduction in ECAD accumulation was observed in *Fgfr1/2* compound *null* mutants (*n=4*). Scale bars, 20 μm.

(C) E-cadherin expression levels were analyzed in the GFP$^+$ *K14-Cre* lineage cells at cell-cell junctions for control and compound *Fgfr1*$^{FCPG/cKO}$*; Fgfr2*$^{cKO/cKO}$ mutants at E15.5 (*n=3)*. Robust ECAD expression between GFP$^+$ *K14 Cre* lineage were observed in both controls and mutants. Normalized mean of integrated fluorescence intensity was plotted as bar graph for control and compound *Fgfr1*$^{FCPG/cKO}$*; Fgfr2*$^{cKO/cKO}$ mutants showing that the introduction of a single *Fgfr1*^{FCPG} allele rescues defect cell-cell adhesion. Scale bars, 20 μm.

Data expressed as mean (+/-SD), * P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001, ns P<0.05 (Student's T-test, two-tailed).

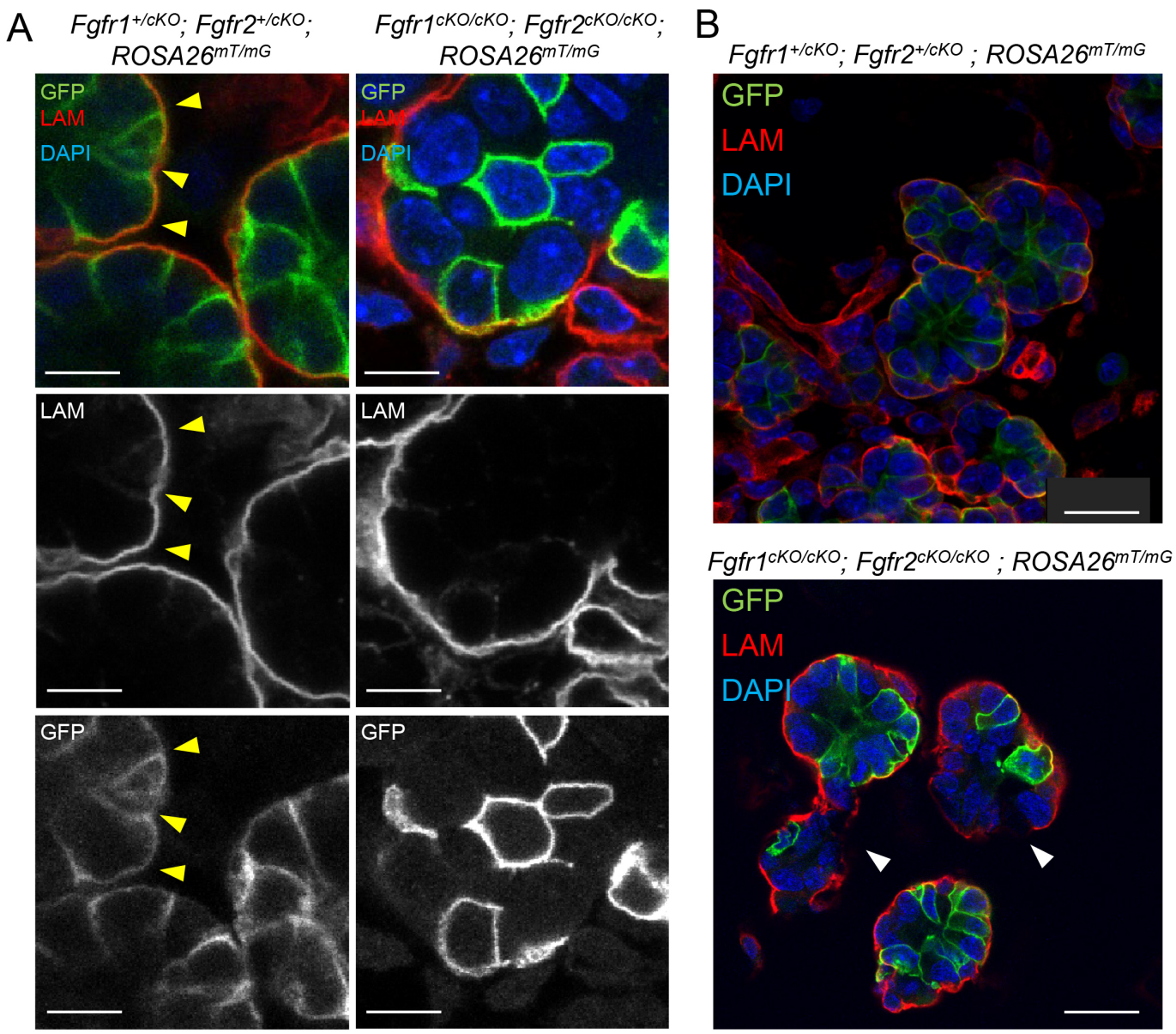
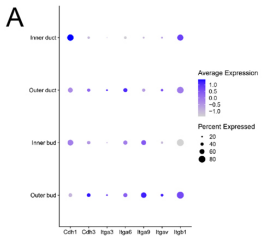
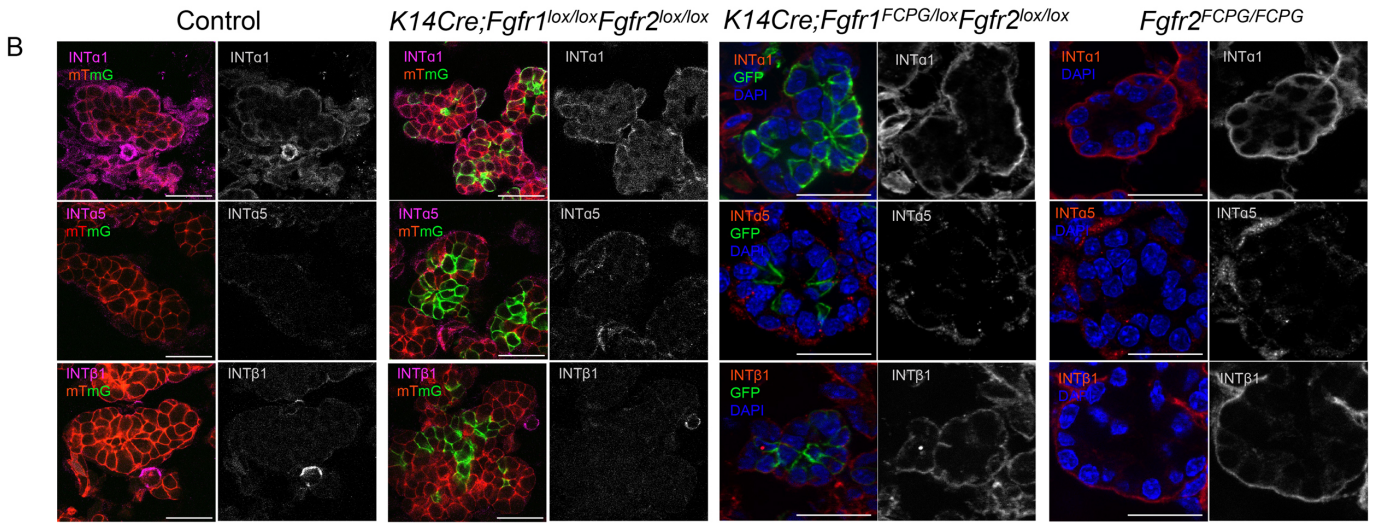


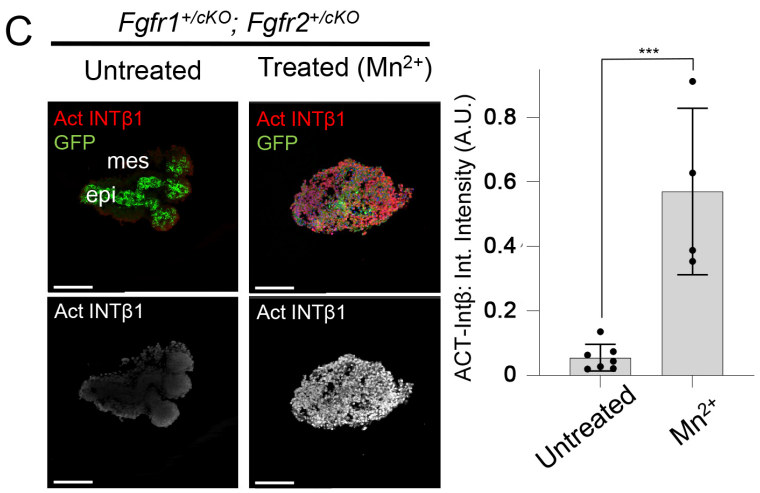
Fig. S5 (related to Fig. 5).

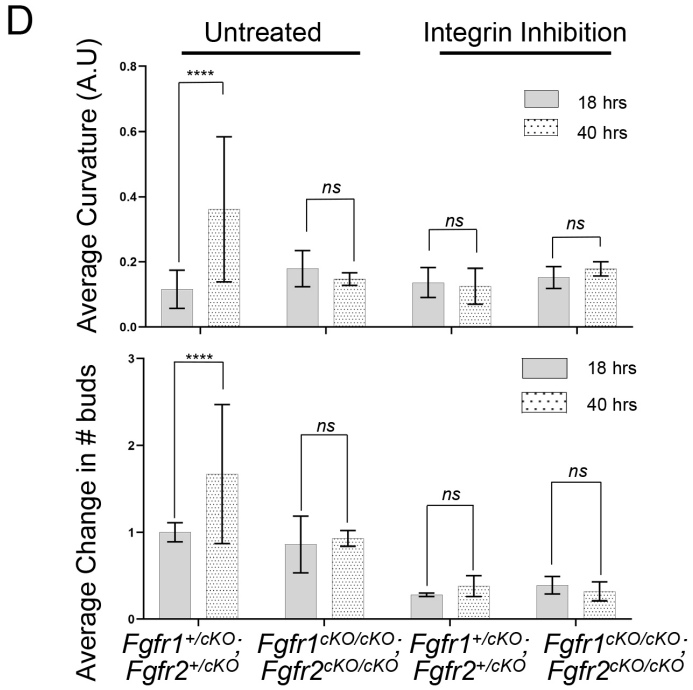
(A) Cell-BM interactions were analyzed in control *Fgfr1*$^{+/cKO}$*; Fgfr2*$^{+/cKO}$ and *Fgfr1*$^{cKO/cKO}$*; Fgfr2*$^{cKO/cKO}$ conditional mutants. *K14* epithelial lineage express GFP, and the BM was marked by Laminin immunofluorescence. Control cells made extensive contacts with the BM at their basal end (yellow arrowheads), whereas this was strongly diminished in double mutants. Scale bars, 10 μm.

(B) The integrity of the basement membrane was analyzed in *Fgfr1/2* compound mutants. Compared to control *Fgfr1*$^{+/cKO}$*; Fgfr2*$^{+/cKO}$ conditional mutants (*n=4)*, *Fgfr1*$^{cKO/cKO}$*; Fgfr2*$^{cKO/cKO}$ conditional mutants (*n=7)* show disintegration of the BM, as visualized by discontinuity in Laminin expression (white arrowheads). Scale bars, 20 μm.









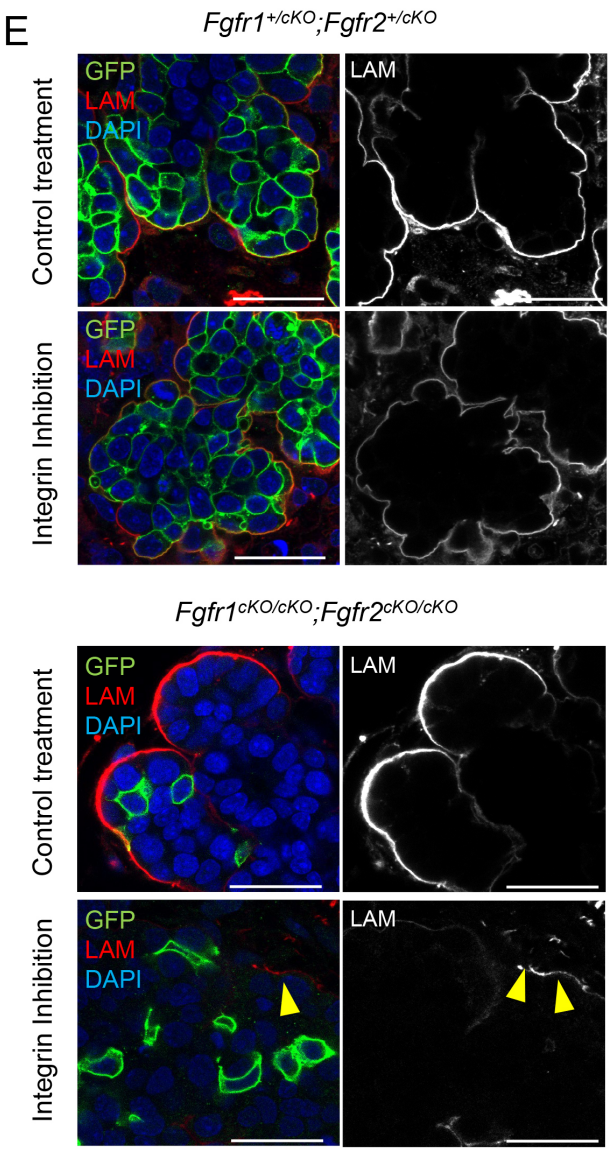


Fig. S6 (related to Fig. 6).

(A) Dot plot showing marker gene expression per cell type and their corresponding expression levels in each cluster from published (GSE159780) scRNA-Seq data, for E13 SMG epithelial cells (Wang et al., 2021). The integrins *Itgb1, Itga9* and *Itga6* show robust upregulation in the outer bud epithelial population.

(B) Integrin α1, α5, and β1 immunofluorescence was used to identify domains within the developing SMGs at E15.5. Integrin levels did not change between control, null mutant and signaling mutant SMGs and was specifically observed on the basal side of outer bud cells. Scale bars 25 μm.

(C) Control *Fgfr1/2*$^{+/cKO}$ mutant SMG explants (E14.5) were treated (n=7 untreated; n=4 treated) with Mn^{2+} to activate integrin signaling ectopically for 8 hrs. Act-INTB1 immunofluorescence was used to measure the extent of integrin activation upon treatment, both in the mesenchyme (mes) and the epithelium (epi-green). Mean integrated immunofluorescence for Act-INTB1 was plotted as a bar graph (error bar represent standard deviation). Robust activation of integrin signaling activation was observed upon Mn^{2+} treatment. Scale bar 200 μm.

(D) The extent of branching was measured by plotting median curvature (error bars represent 95% CI) as bar graphs for SMG explants from various *Fgfr1* and *Fgfr2* compound mutants (E14.5) cultured for 18 and 40 hrs in presence of Mn^{2+} (integrin signaling activation) and compared with untreated controls. Similarly, the average change in number of buds was also plotted as bar graphs (error bars represent standard deviation). Upon activation of integrin signaling, a robust increase in median curvature and an average increase in bud numbers was observed between 18 hrs and 40 hrs across control *Fgfr1*$^{+/cKO}$*; Fgfr2*$^{+/cKO}$ explants. Compound *Fgfr1*$^{cKO/cKO}$*; Fgfr2*$^{cKO/cKO}$ explants did not show a change upon integrin signaling activation.

(E) SMG explants from various *Fgfr1* and *Fgfr2* compound mutants treated with a blocking antibody against integrinβ1 for 40 hrs. Tissues were analyzed on sections. The BM was marked by immunostaining for Laminin. Control *Fgfr1*$^{+/cKO}$*; Fgfr2*$^{+/cKO}$ explants showed robust remodeling of the BM in both untreated and integrin inhibition conditions. *Fgfr1*$^{cKO/cKO}$*; Fgfr2*$^{cKO/cKO}$ mutants showed subtle changes in BM as the Laminin deposition was unequal. Upon inhibition of integrin signaling, negligible Laminin accumulation in the BM was observed. Scale bars, 20 μm.

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001, ns P<0.05 (Two-way ANOVA using Bonferroni multiple comparisons test, two-tailed, or Student's T-test, two-tailed).

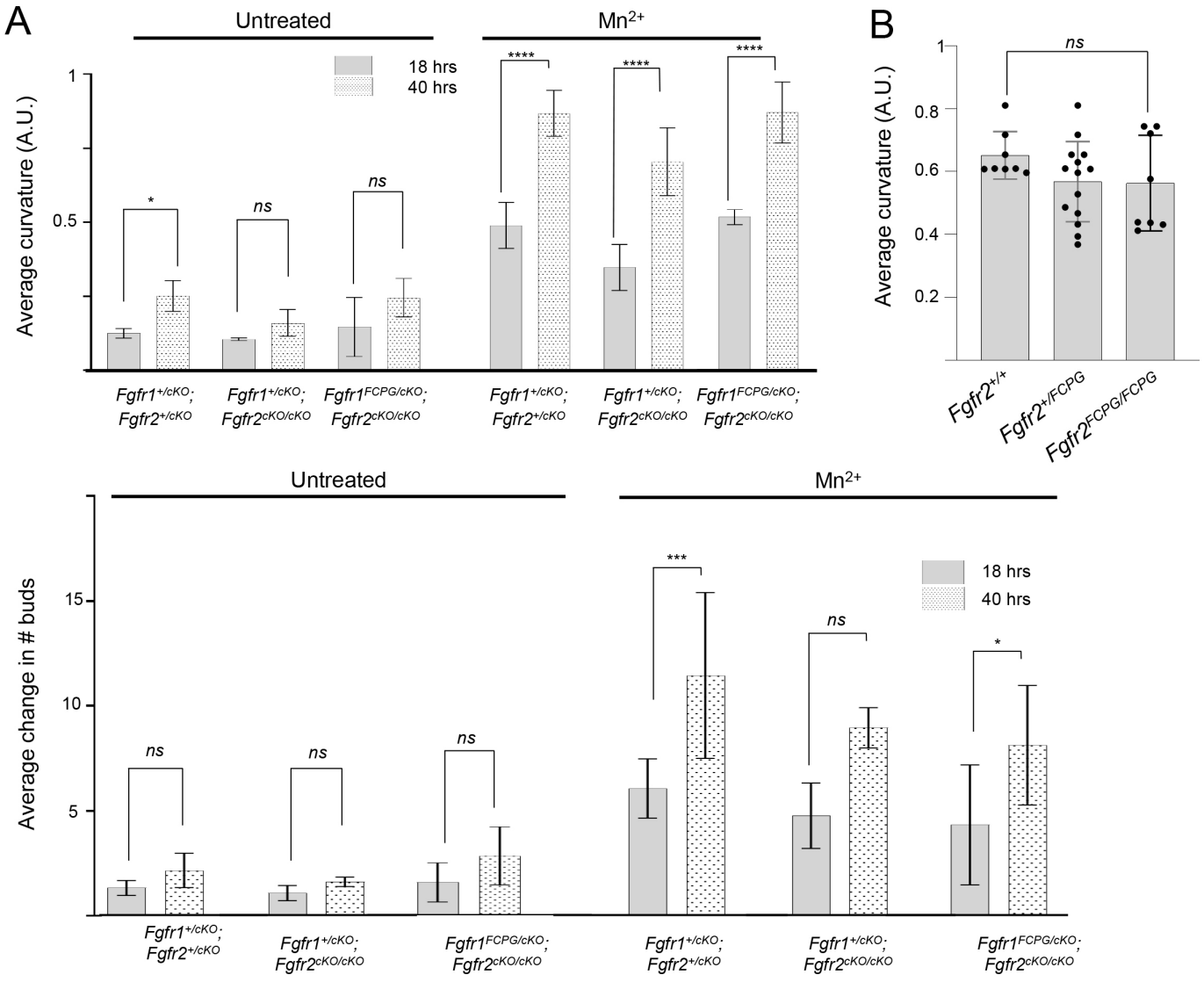


Fig. S7 (related to Fig. 7).

(A) The average curvature during epithelial branching (top) was analyzed in E14.5 SMG explants for control and *Fgfr1/2* compound mutants at 18 hrs and 40 hrs of culture. Median average curvature for *Fgfr1*$^{+/cKO}$; *Fgfr2*$^{+/cKO}$ (*n=8*), *Fgfr1*$^{+/cKO}$; *Fgfr2*$^{cKO/cKO}$ (*n=6*) and *Fgfr1*$^{FCPG/cKO}$; *Fgfr2*$^{cKO/cKO}$ mutants (*n=4*) is represented as bar graphs (error bar represent 95% CI). Similar increases in average curvature were observed at 40 hrs for all categories of mutants. Likewise, integration activation led to an increase in bud numbers (bottom) during epithelial branching for *Fgfr1/2* compound mutants and signaling mutants at 18 hrs and 40 hrs during culture (error bars represent standard deviations).

(B) The median of average curvature is plotted as bar graphs for control *Fgfr2*$^{+/+}$ and *Fgfr2*$^{+/-}$ SMG and compared with *Fgfr2*$^{FCPG/FCPG}$ SMG explants. Tissues were cultured for 40 hrs upon Mn2+ treatment.

* P<0.05, ** P<0.01, *** P<0.001, **** P<0.0001, ns P<0.05 (One-way or Two-way ANOVA using Bonferroni multiple comparisons test, two-tailed).