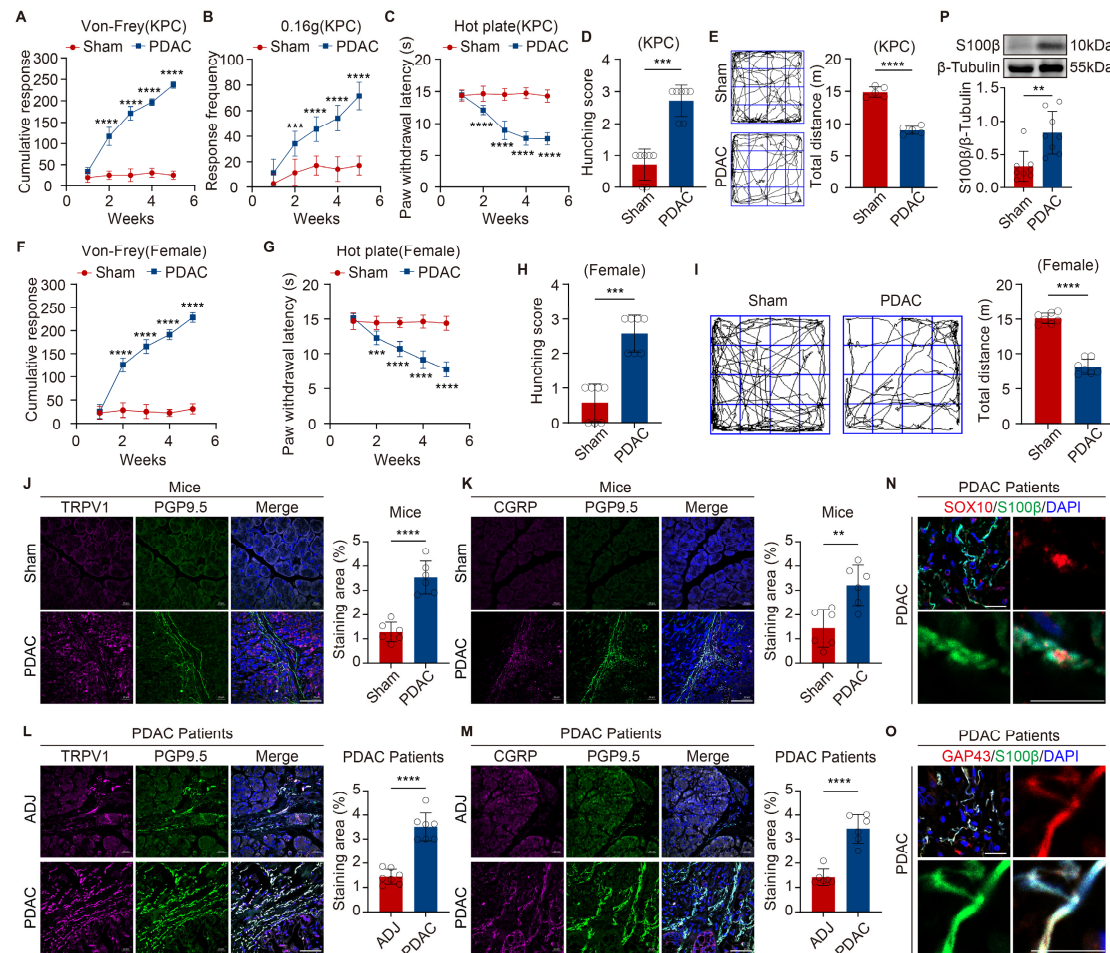


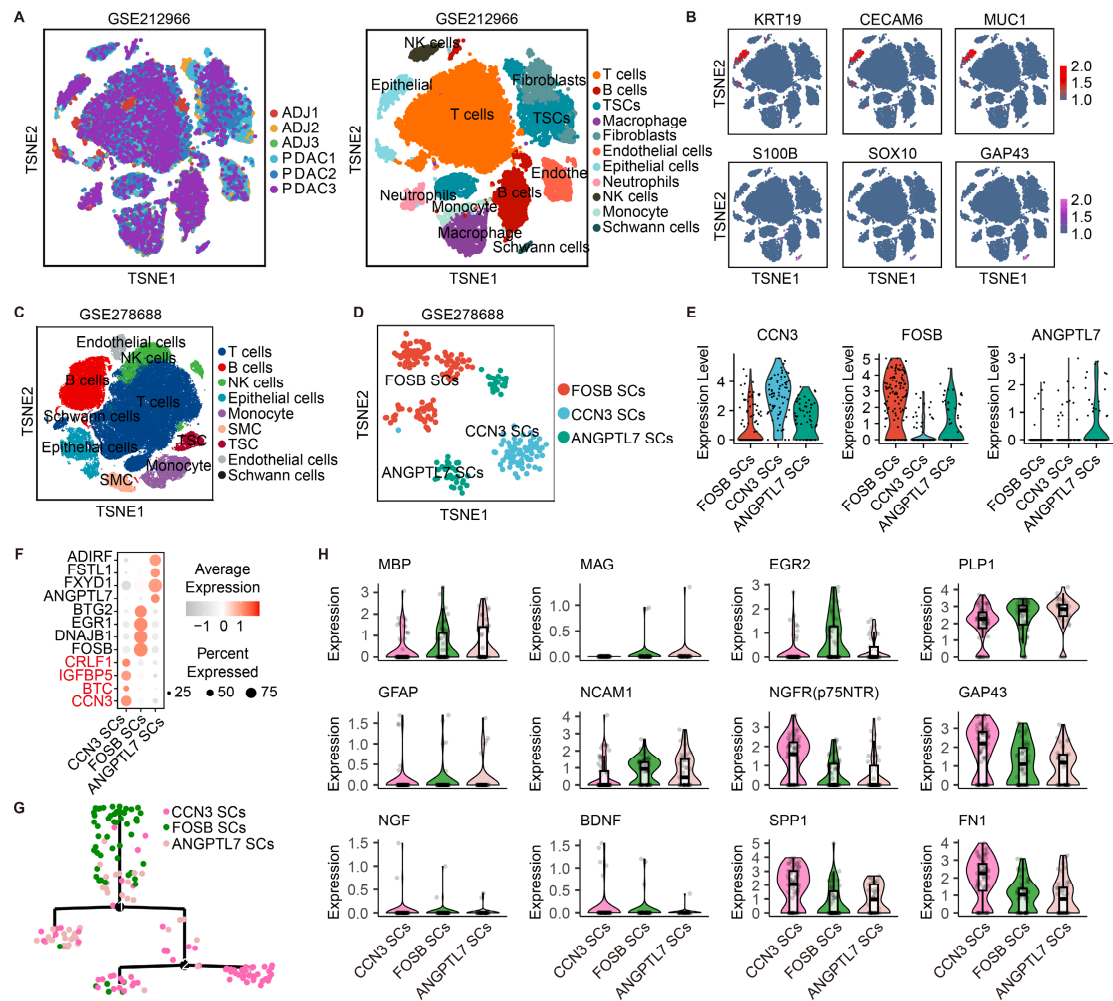
Tumor-derived GDF15 induces CCN3⁺ Schwann cells to promote cancer pain in pancreatic cancer

Supplementary Figures



Supplementary Fig. 1 | Persistent chronic pain in PDAC mice and increased TRPV1⁺/CGRP⁺ fibers in PDAC. A-E The syngeneic KPC PDAC cancer cells were injected into the pancreas in situ and the painful behavior of was evaluated by detecting spontaneous pain (hunching score at week 5) in mice, movement restriction (total distance traveled at week 5), mechanical allodynia (cumulative withdrawal response and response frequency measured weekly) and thermal hyperalgesia (the paw withdrawal latency to heat measured weekly). (A) two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: **** $P < 0.0001$ vs. Sham group. $n = 7$ mice per group. (B) two-way repeated measures ANOVA. Šidák's post hoc test for multiple

comparisons: *** $P < 0.001$, **** $P < 0.0001$ vs. Sham group. $n = 7$ mice per group. **(C)** two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: **** $P < 0.0001$ vs. Sham group. $n = 7$ mice per group. **(D)** Mann-Whitney U test. *** $P < 0.001$ vs. Sham group. $n = 7$ mice per group. **(E)** unpaired t test. **** $P < 0.0001$ vs. Sham group. $n = 5$ mice per group. **F-I** The syngeneic K8484 PDAC cancer cells were injected into the pancreas of female mice in situ and the painful behavior of was evaluated by detecting spontaneous pain (hunching score at week 5) in mice, movement restriction (total distance traveled at week 5), mechanical allodynia (cumulative withdrawal response measured weekly) and thermal hyperalgesia (the paw withdrawal latency to heat measured weekly). **(F)** two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: **** $P < 0.0001$ vs. Sham group. $n = 7$ mice per group. **(G)** two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: *** $P < 0.001$, **** $P < 0.0001$ vs. Sham group. $n = 7$ mice per group. **(H)** Mann-Whitney U test. *** $P < 0.001$ vs. Sham group. $n = 7$ mice per group. **(I)** unpaired t test. **** $P < 0.0001$ vs. Sham group. $n = 7$ mice per group. **J, K** Representative double immunofluorescence staining and quantification showed the colocalization of TRPV1 and PGP9.5 or CGRP and PGP9.5 in sham group pancreas and pancreatic tumor of PDAC mice. Scale bars: 50 μm . **(J)** unpaired t test. **** $P < 0.0001$ vs. Sham group. $n = 6$ mice per group. **(K)** unpaired t test. ** $P < 0.01$ vs. Sham group. $n = 6$ mice per group. **L, M** Representative immunofluorescence staining and quantification showed the colocalization of TRPV1 and PGP9.5 or CGRP and PGP9.5 in the adjacent normal tissue and pancreatic tumor in PDAC patients. Scale bars: 50 μm . **(L)** unpaired t test. **** $P < 0.0001$ vs. ADJ group. $n = 7$ patients per group. **(M)** unpaired t test. **** $P < 0.0001$ vs. ADJ group. $n = 7$ patients per group. **N, O** Representative double immunofluorescence staining showed the colocalization of S100 β and SOX10, or S100 β and GAP43 in the pancreatic tumor in PDAC patients ($n = 5$ patients). Scale bars: 50 μm . **P** Representative immunoblot images showing the protein level of S100 β in sham group pancreas and pancreatic tumor of PDAC mice. unpaired t test. Cohen's $d = 1.888$. 95% CI [-0.804—0.209]. ** $P = 0.0026$ vs. sham group. $n = 8$ mice per group. Data are shown as the mean $\pm$ SEM. ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. Source data are provided as a Source Data file.



Supplementary Fig. 2 | Identification of CCN3⁺ SCs in PDAC from the GEO public database.

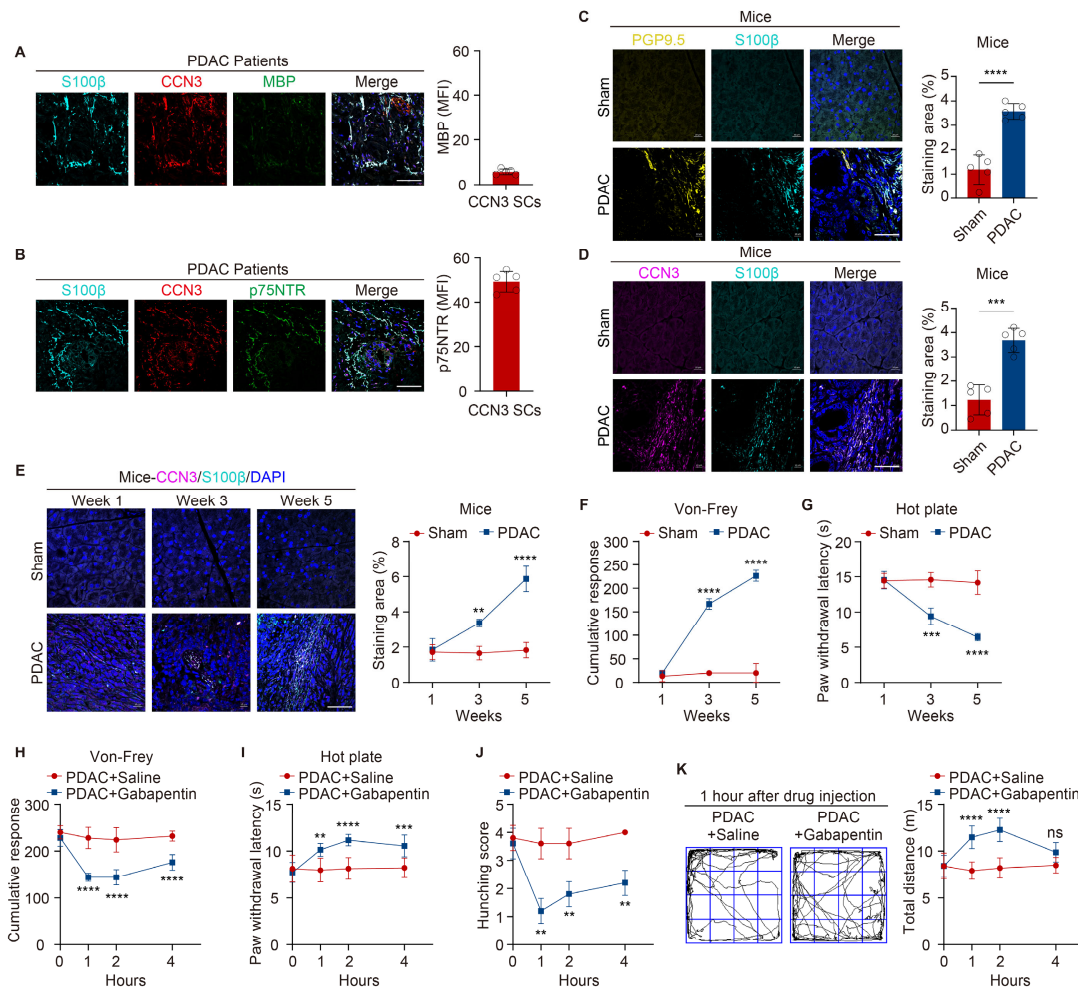
A Identifications of 11 cell clusters from single-cell sequencing dataset of patients from the GEO public database (GSE212966) (adjacent normal tissues and tumor tissues from 3 PDAC patients).

B Epithelial cells were identified by labeling *Krt19*, *Ceacam6* and *Muc1*, and SCs were identified by labeling *S100B*, *Sox10* and *Gap43* from single-cell sequencing dataset of patients from the GEO public database (GSE212966) (adjacent normal tissues and tumor tissues from 3 PDAC patients).

C Identifications of 9 cell clusters from single-cell sequencing dataset of patients from another GEO public database (GSE278688). **D-E** Identifications of 3 subclusters of SCs from single-cell sequencing dataset of patients (GSE278688) from the GEO public database.

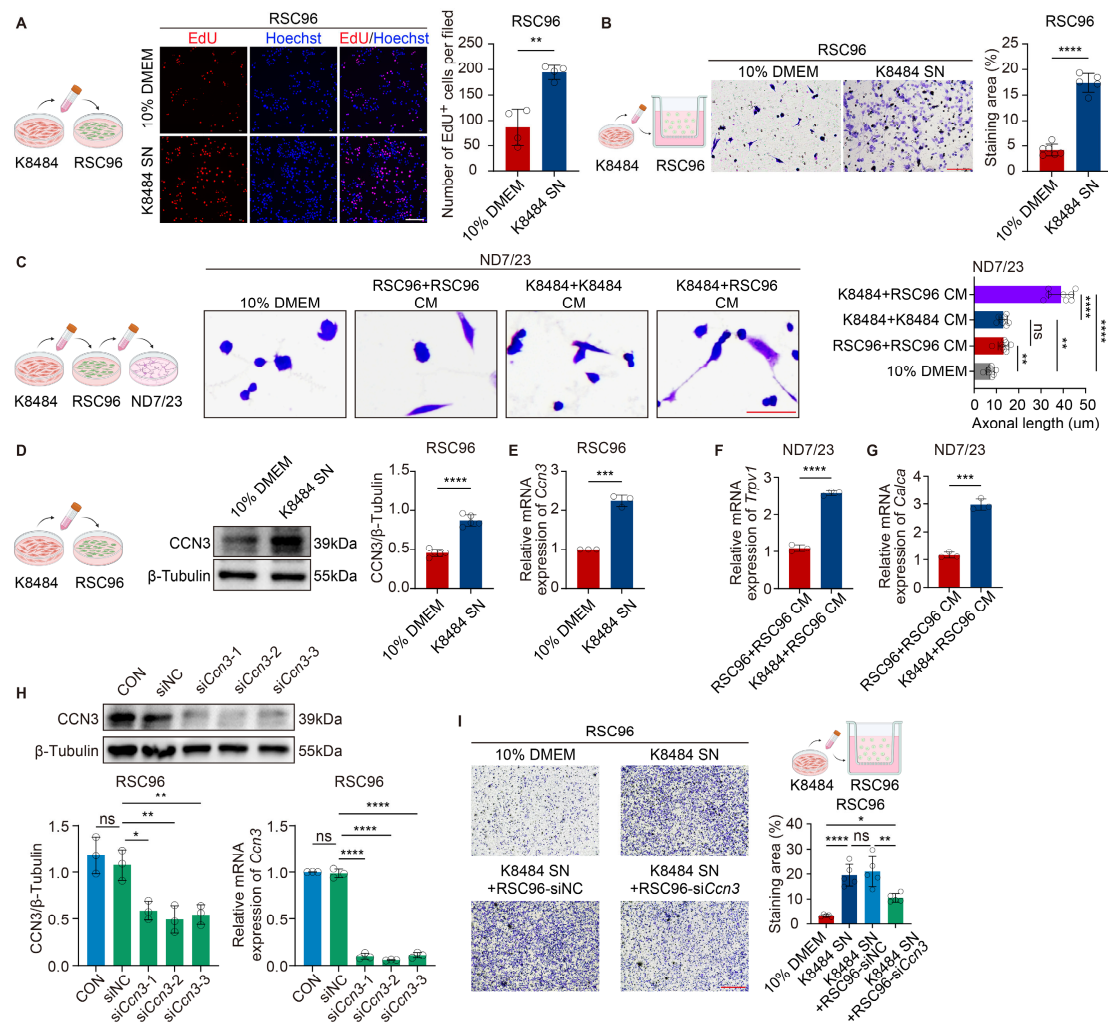
F Gene expression heatmap showed the characteristic genes of 3 Schwann cell subclusters including CCN3⁺ SCs, FOSB⁺ SCs and ANGPTL7⁺ SCs in adjacent normal tissues and tumor tissues from single-cell sequencing dataset of PDAC patients (GSE212966). **G** Cell trajectory analysis of CCN3⁺ SCs from single-cell sequencing dataset of PDAC patients (GSE212966). **H** Expression of myelinating

Schwann cell-related genes (*Mbp*, *Mag*, *Egr2*), non-myelinating Schwann cell-related genes (*Plp1*, *Gfap*, *Ncam1*), repair-associated Schwann cell genes (*Ngfr*, *Gap43*), as well as neurotrophic factors and cytokines (*Ngf*, *Bdnf*, *Spp1*, *Fn1*) in Schwann cell subsets from the GEO public database (GSE212966). Source data are provided as a Source Data file.



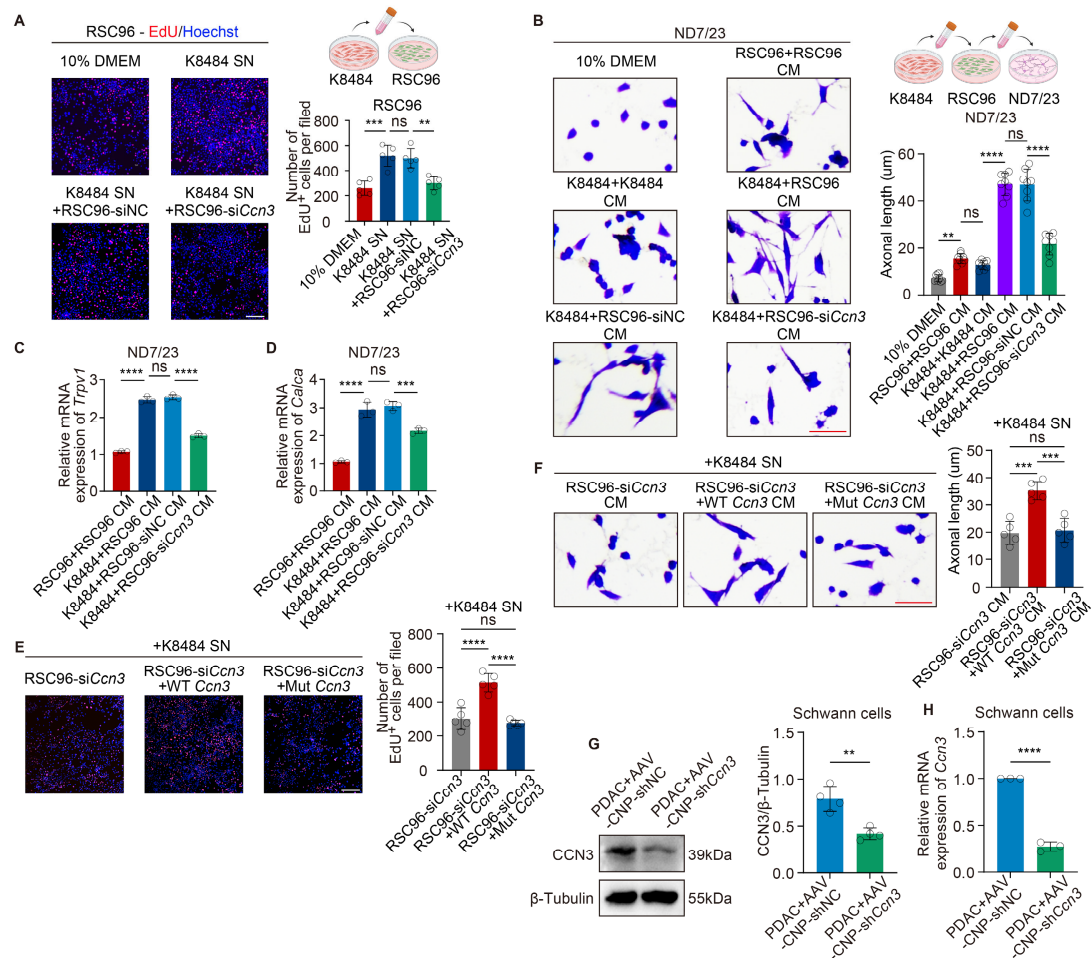
Supplementary Fig. 3 | Increased CCN3⁺ SCs correlate with PDAC pain. **A** Representative immunofluorescence staining and analysis showed the colocalization of MBP, CCN3 and S100 β in the pancreatic tumor in PDAC patients ($n = 5$ patients). Scale bars: 50 μ m. **B** Representative immunofluorescence staining and analysis showed the colocalization of p75NTR, CCN3 and S100 β in the pancreatic tumor in PDAC patients ($n = 5$ patients). Scale bars: 50 μ m. **C** Representative immunofluorescence staining and quantification showed the colocalization of PGP9.5 and S100 β in the sham mice pancreas and pancreatic tumor of KPC mice. Scale bars: 50 μ m. unpaired t test. **** $P < 0.0001$ vs. Sham group. $n = 5$ mice per group. **D** Representative immunofluorescence staining and quantification showed the colocalization of CCN3 and S100 β in the sham mice pancreas and pancreatic tumor of KPC mice. Scale bars: 50 μ m. unpaired t test. *** $P < 0.001$ vs. Sham group. $n = 5$ mice per group. **E** Representative double immunofluorescence staining and quantification showed the colocalization of CCN3 and S100 β in sham group pancreas and pancreatic tumor of PDAC mice at week 1, 3, 5. Scale bars: 50 μ m. two-way repeated measures ANOVA.

Šidák's post hoc test for multiple comparisons: $**P < 0.01$, $****P < 0.0001$ vs. Sham group. $n = 3$ mice per group. **F-G** The painful behavior was evaluated by detecting mechanical allodynia (cumulative withdrawal response) and thermal hyperalgesia (the paw withdrawal latency to heat) at week 1, 3, 5. two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: $***P < 0.001$, $****P < 0.0001$ vs. Sham group. $n = 3$ mice per group. **H-K** Mechanical allodynia, thermal hyperalgesia, spontaneous pain and movement restriction in PDAC mice after gabapentin treatment. **(H)** two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: $****P < 0.0001$ vs. Saline group. $n = 5$ mice per group. **(I)** two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$ vs. Saline group. $n = 5$ mice per group. **(J)** Mann-Whitney U test. $**P < 0.01$ vs. Saline group. $n = 5$ mice per group. **(K)** two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: $****P < 0.0001$ vs. Saline group. $n = 5$ mice per group. Data are shown as the mean $\pm$ SEM. ns, not significant, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$. Source data are provided as a Source Data file.



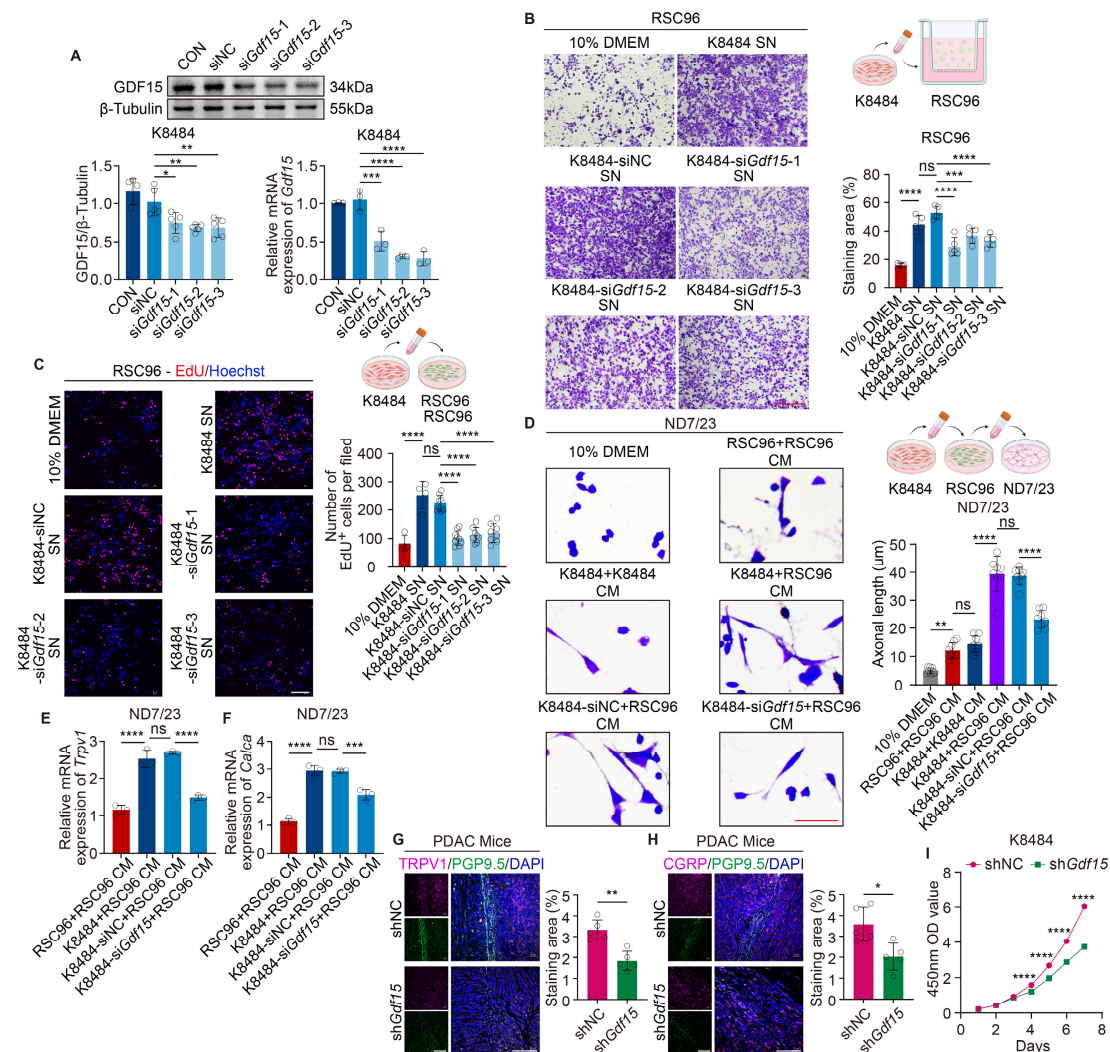
Supplementary Fig. 4 | In vitro cancer cells stimulate the proliferation of CCN3⁺ SCs, thereby promoting nerve fiber growth and sensitization. **A** Representative proliferation staining and quantification showing the number of EdU-positive cells in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant. Scale bars: 500 μ m. unpaired t test. ** $P < 0.01$ vs. 10% DMEM group. $n = 4$ independent experiments per group. The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **B** Representative migration staining and quantification showing the migrating of RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant. Scale bars: 100 μ m. unpaired t test. **** $P < 0.0001$ vs. 10% DMEM group. $n = 6$ independent experiments (10% DMEM), $n = 5$ independent experiments (K8484 SN). The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **C** Representative staining images and the quantification of fiber length of ND7/23 cells following the incubation with 10%DMEM or the conditioned medium from

the co-culture of K8484 cells and RSC96 cells. Scale bars: 50 μ m. one-way ANOVA with Tukey's post hoc test for multiple comparisons. K8484+RSC96 CM vs. RSC96+RSC96 CM: **** $P < 0.0001$. $n = 8$ independent experiments per group. The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **D** Representative immunoblot images showing the protein level of CCN3 in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant. unpaired t test. **** $P < 0.0001$ vs. 10% DMEM group. $n = 5$ independent experiments per group. The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **E** the *Ccn3* mRNA expression in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant. unpaired t test. *** $P < 0.001$ vs. 10% DMEM group. $n = 3$ independent experiments per group. **F, G** The *Trpv1* and *Calca* mRNA expression in ND7/23 cells after exposure to conditioned medium from the co-culture of K8484 cells and RSC96 cells. unpaired t test. *** $P < 0.001$, **** $P < 0.0001$ vs. RSC96+RSC96 group. $n = 3$ independent experiments per group. **H** The CCN3 protein and mRNA levels in RSC96 cells treated with si*Ccn3* or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. * $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$ vs. siNC group. $n = 3$ independent experiments per group. **I** Representative migration staining and quantification showing the migrating of RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant treated with si*Ccn3* or scrambled siRNA. Scale bars: 100 μ m. one-way ANOVA with Tukey's post hoc test for multiple comparisons. si*Ccn3* vs. siNC: ** $P < 0.01$. $n = 5$ independent experiments per group. The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. Data are shown as the mean $\pm$ SEM. ns, not significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. Source data are provided as a Source Data file.



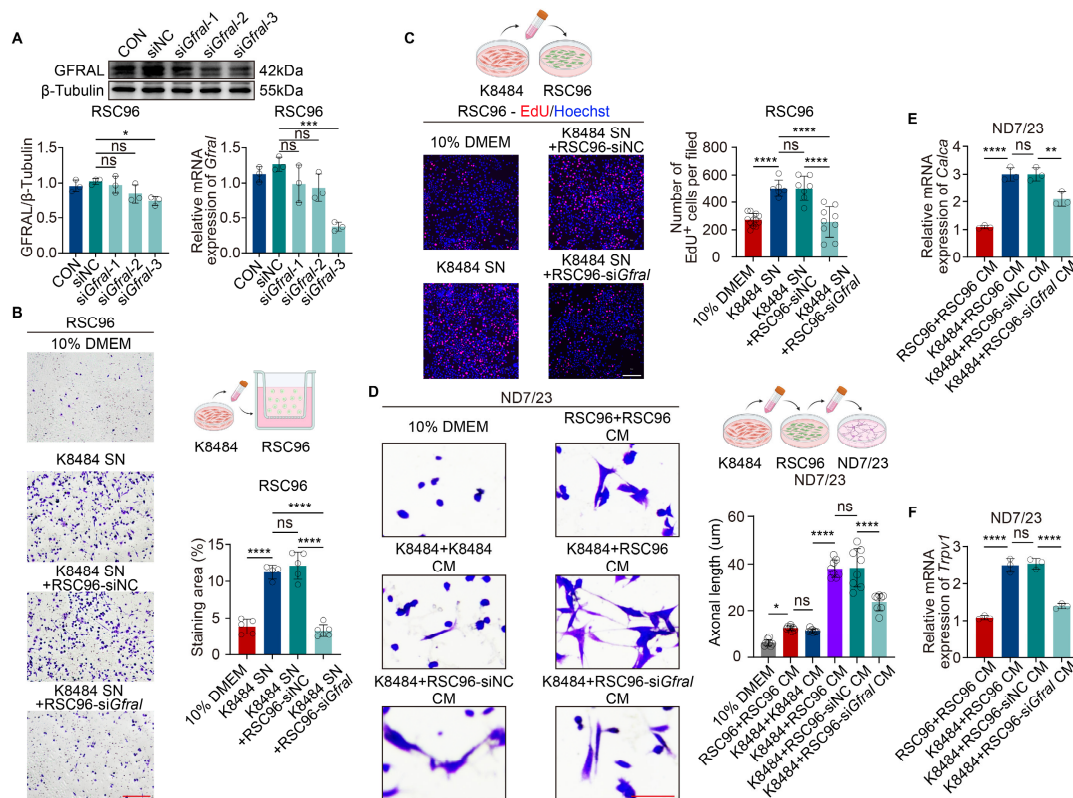
Supplementary Fig. 5 | CCN3 is essential for driving Schwann cell proliferation, nerve fiber growth and sensitization. **A** Representative proliferation staining and quantification showing the number of EdU-positive cells in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant treated with siCcn3 or scrambled siRNA. Scale bars: 500 μm. one-way ANOVA with Tukey's post hoc test for multiple comparisons. siCcn3 vs. siNC: ** $P < 0.01$. $n = 5$ independent experiments per group. The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **B** Representative staining and the quantification of fiber length of ND7/23 cells following the incubation with the conditioned medium from the co-culture of K8484 cells and RSC96 cells treated with siCcn3. Scale bars: 50 μm. one-way ANOVA with Tukey's post hoc test for multiple comparisons. siCcn3 vs. siNC: **** $P < 0.0001$. $n = 8$ independent experiments per group. The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **C, D** The *Trpv1* and *Calca* mRNA expression in ND7/23 cells after exposure to conditioned medium from the co-culture of siCcn3-treated K8484 cells and RSC96 cells.

one-way ANOVA with Tukey's post hoc test for multiple comparisons. si*Ccn3* vs. siNC: *** $P < 0.001$, **** $P < 0.0001$. $n = 3$ independent experiments per group. **E** Representative proliferation staining and quantification showing the number of EdU-positive cells in si*Ccn3*-treated RSC96 cells following the incubation of K8484 cell supernatant and transfection of wild-type *Ccn3* or mutant *Ccn3*. Scale bars: 500 μm . one-way ANOVA with Tukey's post hoc test for multiple comparisons. si*Ccn3*+WT *Ccn3* vs. si*Ccn3*: **** $P < 0.0001$. si*Ccn3*+Mut *Ccn3* vs. si*Ccn3*+WT *Ccn3*: **** $P < 0.0001$. $n = 5$ independent experiments per group. **F** Representative staining and the quantification of fiber length of ND7/23 cells following the incubation with the conditioned medium from the co-culture of K8484 cells and si*Ccn3*-treated RSC96 cells after transfection of wild-type *Ccn3* or mutant *Ccn3*. Scale bars: 50 μm . one-way ANOVA with Tukey's post hoc test for multiple comparisons. si*Ccn3*+WT *Ccn3* vs. si*Ccn3*: *** $P < 0.001$. si*Ccn3*+Mut *Ccn3* vs. si*Ccn3*+WT *Ccn3*: *** $P < 0.001$. $n = 5$ independent experiments per group. **G, H** The protein and mRNA levels of CCN3 in tumor-infiltrating SCs isolated by fluorescence-activated cell sorting from PDAC mice following intratumoral injection of AAV-CNP-sh*Ccn3*. unpaired t test. ** $P < 0.01$, **** $P < 0.0001$ vs. shNC group. $n = 4$ mice per group (protein), $n = 3$ mice per group (mRNA). The gating strategy is shown in Supplementary Fig. 15. Data are shown as the mean $\pm$ SEM. ns, not significant, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. Source data are provided as a Source Data file.



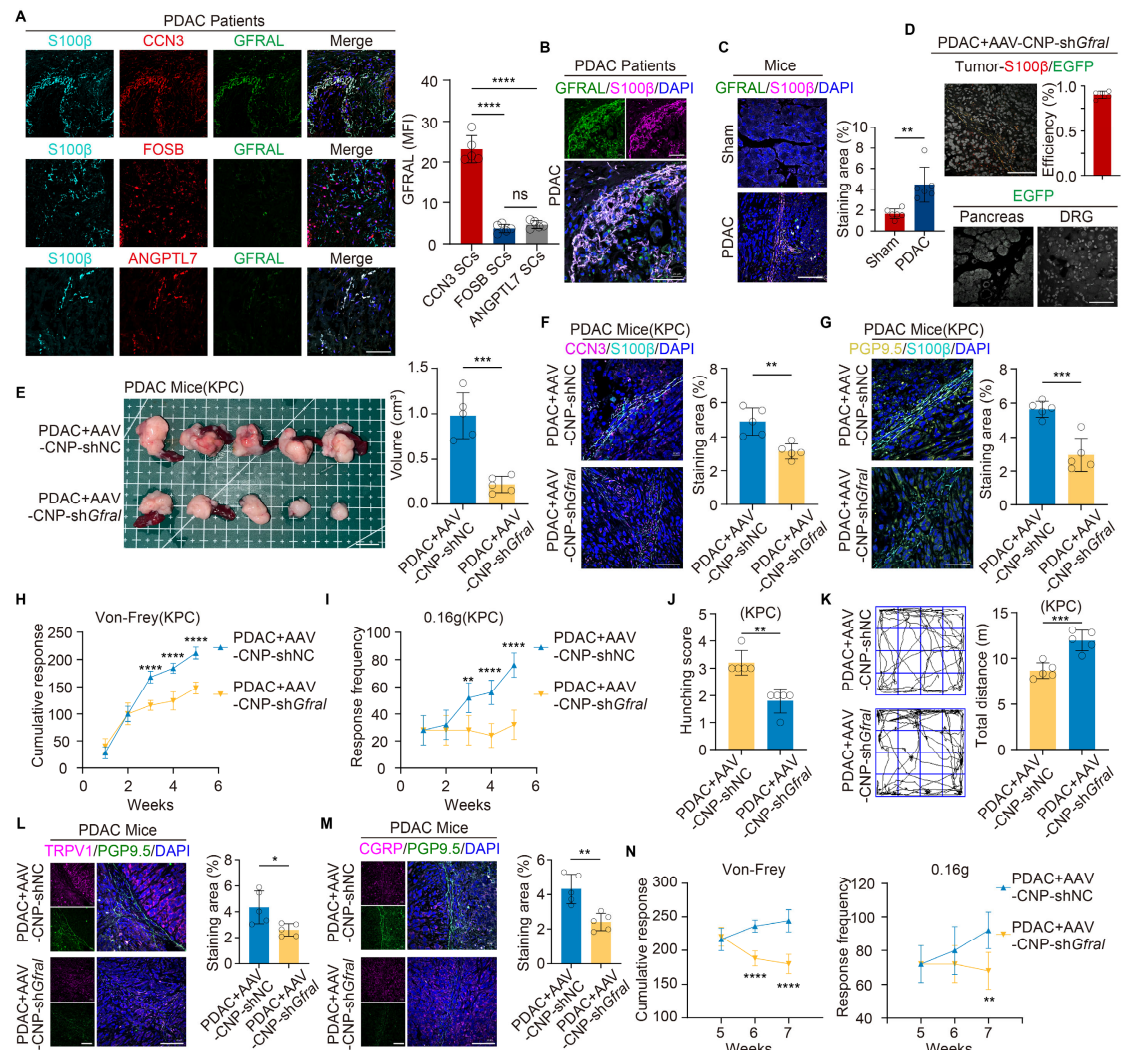
Supplementary Fig. 7 | The GDF15 knockdown in cancer cells inhibits the proliferation of CCN3⁺ SCs, nerve fiber growth and sensitization. **A** The GDF15 mRNA and protein levels in K8484 cells treated with siGdf15 or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ vs. siNC group. $n = 5$ independent experiments per group (protein), $n = 3$ independent experiments per group (mRNA) **B** siGdf15 inhibited the migrating of RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant. Scale bars: 100 μ m. one-way ANOVA with Tukey's post hoc test for multiple comparisons. *** $P < 0.001$, **** $P < 0.0001$ vs. siNC group. $n = 5$ independent experiments per group. The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **C** Representative proliferation staining and quantification showed the number of EdU-positive cells in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant treated with siGdf15 or scrambled siRNA. Scale bars: 500 μ m. one-way ANOVA

with Tukey's post hoc test for multiple comparisons. **** $P < 0.0001$ vs. siNC group. $n = 4$ independent experiments per group (10% DMEM, K8484 SN), $n = 8$ independent experiments per group (siNC, si*Gdf15*). The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **D** The fiber length of ND7/23 cells was examined following the incubation with the conditioned medium from the co-culture of RSC96 cells and K8484 cells treated with si*Gdf15* (one-way ANOVA test, $n = 15$ biological replicates). Scale bars: 50 μm . one-way ANOVA with Tukey's post hoc test for multiple comparisons. **** $P < 0.0001$ vs. siNC group. $n = 8$ independent experiments per group. The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **E, F** The *Trpv1* and *Calca* mRNA expression in ND7/23 cells after exposure to conditioned medium from the co-culture of si*Gdf15*-treated K8484 cells and RSC96 cells. one-way ANOVA with Tukey's post hoc test for multiple comparisons. *** $P < 0.001$, **** $P < 0.0001$ vs. siNC group. $n = 3$ independent experiments per group **G, H** Representative double staining and quantification showed the pre-application of sh*Gdf15* on K8484 cells inhibited the colocalization of TRPV1 and PGP9.5 or CGRP and PGP9.5 in pancreatic tumor of PDAC mice. Scale bars: 50 μm . unpaired t test. * $P < 0.05$, ** $P < 0.01$ vs. shNC group. $n = 5$ mice per group **I** CCK8 proliferation curve of K8484 cells treated with sh*Gdf15* or scramble shRNA. two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: **** $P < 0.0001$ vs. shNC group. $n = 5$ independent experiments per group. Data are shown as the mean $\pm$ SEM. ns, not significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. Source data are provided as a Source Data file.



Supplementary Fig. 8 | GFRAL inhibition reverses cancer-induced CCN3⁺ SCs proliferation, nerve fiber growth and sensitization. **A** The GFRAL mRNA and protein levels in RSC96 cells treated with siGfral or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. * $P < 0.05$, *** $P < 0.001$ vs. siNC group. $n = 3$ independent experiments per group. **B** Representative migration staining and quantification showing the migrating of RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant treated with siGfral or scrambled siRNA. Scale bars: 100 μ m. one-way ANOVA with Tukey's post hoc test for multiple comparisons. **** $P < 0.0001$ vs. siNC group. $n = 5$ independent experiments per group. The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **C** Representative proliferation staining and quantification showing the number of EdU-positive cells in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant treated with siGfral or scrambled siRNA. Scale bars: 500 μ m. one-way ANOVA with Tukey's post hoc test for multiple comparisons. **** $P < 0.0001$ vs. siNC group. $n = 7$ independent experiments per group (siNC), $n = 9$ independent experiments per group (siGfral). The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d251889>. **D** Representative staining of ND7/23 cells following the incubation with the conditioned medium from the co-culture of K8484 cells and RSC96 cells treated

with *siGfrol*. Scale bars: 50 μ m. one-way ANOVA with Tukey's post hoc test for multiple comparisons. **** $P < 0.0001$ vs. siNC group. $n = 8$ independent experiments per group. The schematic diagram was created in BioRender. Guojun, C. (2026) <https://BioRender.com/d25l889>. **E, F** The *Trpv1* and *Calca* mRNA expression in ND7/23 cells after exposure to conditioned medium from the co-culture of K8484 cells and *siGfrol*-treated RSC96 cells. one-way ANOVA with Tukey's post hoc test for multiple comparisons. ** $P < 0.01$, **** $P < 0.0001$ vs. siNC group. $n = 3$ independent experiments per group. Data are shown as the mean $\pm$ SEM. ns, not significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. Source data are provided as a Source Data file.



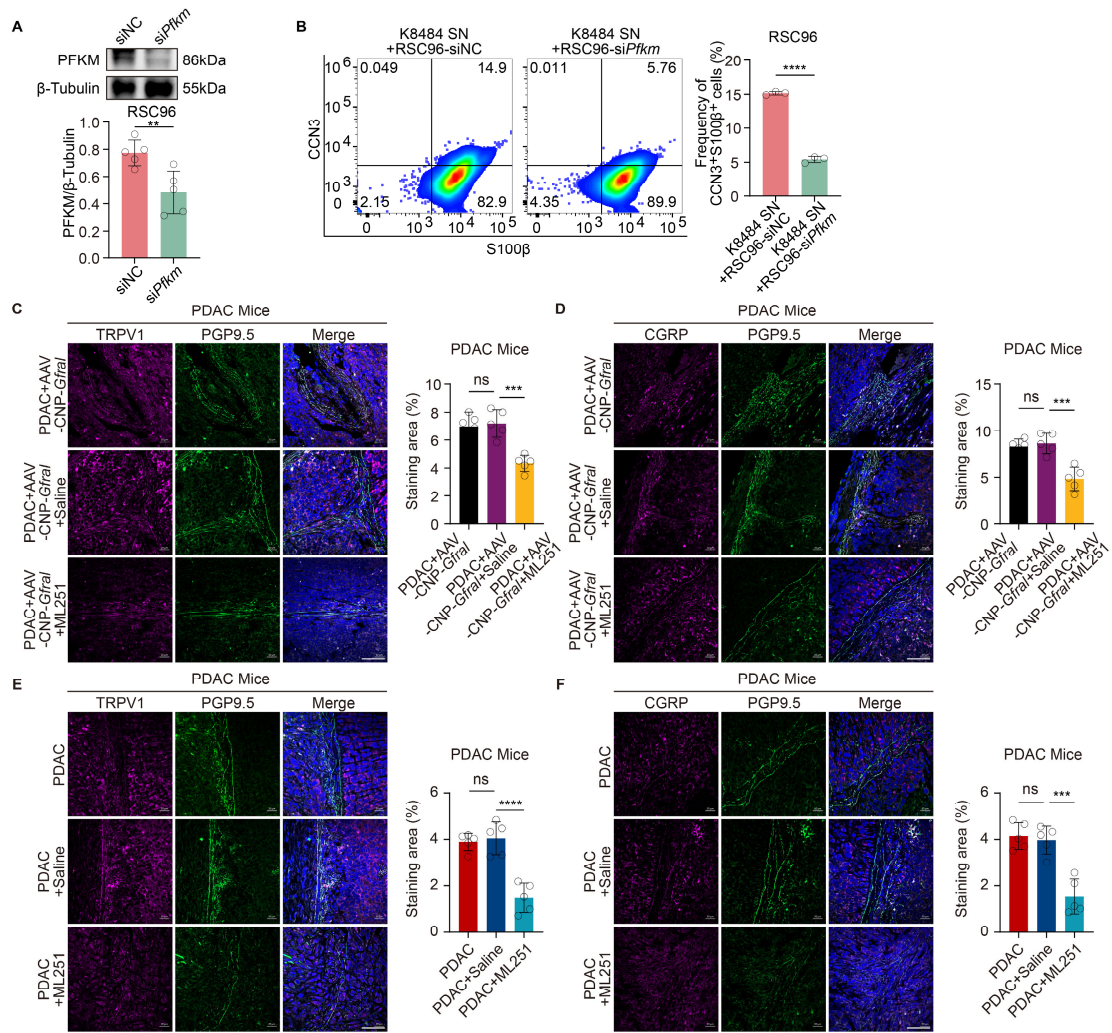
Supplementary Fig. 9 | GFRAL expression in SCs and its mediation of pain in KPC mice. A

Representative immunofluorescence staining and analysis showed the expression of GFRAL in three Schwann cell subpopulations the pancreatic tumor in PDAC patients. Scale bars: 50 μ m. one-way ANOVA with Tukey's post hoc test for multiple comparisons. CCN3⁺ SCs vs. FOSB⁺ SCs: **** $P < 0.0001$, CCN3⁺ SCs vs. ANGPTL7⁺ SCs: **** $P < 0.0001$. $n = 5$ patients per group. **B**

Representative staining showed the colocalization of GFRAL and S100 β in the pancreatic tumor of PDAC patients ($n = 5$ patients). Scale bars: 50 μ m. **C** Representative double staining and quantification showed that the colocalization of GFRAL and S100 β was increased in pancreatic tumor of PDAC mice. Scale bars: 50 μ m. unpaired t test. ** $P < 0.01$ vs. Sham group. $n = 6$ mice per group. **D** Representative staining showing the expression of AAV-encoded EGFP and S100 β

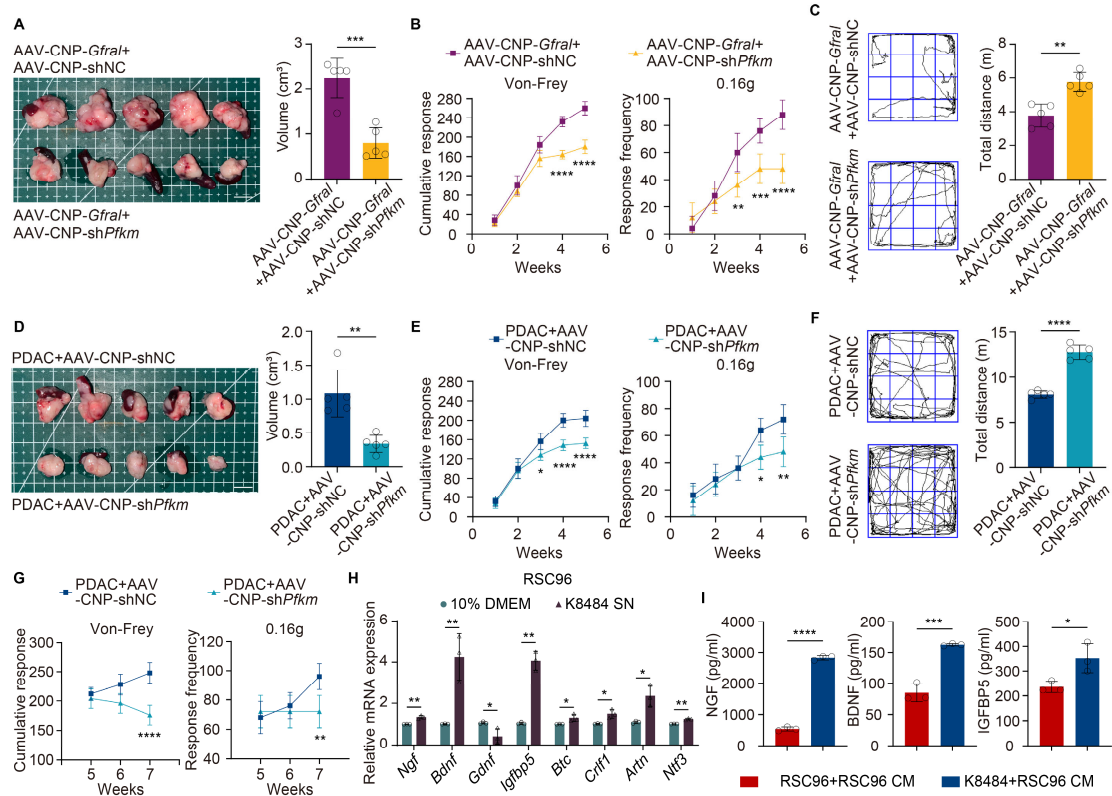
fluorescence in tumor, pancreas and DRG tissues following intratumoral injection of AAV-CNP-shGfral ($n = 5$ mice). Scale bars: 50 μ m. **E** The syngeneic KPC PDAC cancer cells were injected

into the pancreas in situ. Specimen diagrams and quantification showing the KPC pancreatic tumor of mice following the intratumoral injection of AAV-CNP-sh*Gfral* or AAV-CNP-scrambled shRNA. Scale bars: 1 cm. unpaired t test. *** $P < 0.001$ vs. shNC group. $n = 5$ mice per group. **F** Representative staining and quantification showed that intratumoral injection of AAV-CNP-sh*Gfral* inhibited the increased colocalization of CCN3 and S100 β in pancreatic tumor of KPC PDAC mice. Scale bars: 50 μm . unpaired t test. ** $P < 0.01$ vs. shNC group. $n = 5$ mice per group. **G** Representative immunofluorescence staining and quantification showed that inhibition of GFRAL by using AAV-CNP-sh*Gfral* prevented the increased co-expression of the PGP9.5 and S100 β in pancreatic tumor of KPC PDAC mice. Scale bars: 50 μm . unpaired t test. *** $P < 0.001$ vs. shNC group. $n = 5$ mice per group. **H-K** Mechanical allodynia, spontaneous pain and movement restriction in KPC PDAC mice after intratumoral injection of AAV-CNP-sh*Gfral* or AAV-CNP-scrambled shRNA. (**H**) two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: **** $P < 0.0001$ vs. shNC group. $n = 5$ mice per group. (**I**) two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: ** $P < 0.01$, **** $P < 0.0001$ vs. shNC group. $n = 5$ mice per group. (**J**) Mann-Whitney U test. ** $P < 0.01$ vs. shNC group. $n = 5$ mice per group. (**K**) unpaired t test. *** $P < 0.001$ vs. Sham group. $n = 5$ shNC per group. **L, M** Representative staining and quantification showed that intratumoral injection of AAV-CNP-sh*Gfral* inhibited the increased colocalization of TRPV1 and PGP9.5 or CGRP and PGP9.5 in pancreatic tumor of K8484 PDAC mice. Scale bars: 50 μm . unpaired t test. * $P < 0.05$, ** $P < 0.01$ vs. shNC group. $n = 5$ mice per group. **N** Mechanical allodynia in PDAC mice following intratumoral injection of AAV-CNP-sh*Gfral* or AAV-CNP-scrambled shRNA at week 5. two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: ** $P < 0.01$, **** $P < 0.0001$ vs. shNC group. $n = 5$ mice per group. Data are shown as the mean $\pm$ SEM. ns, not significant, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. Source data are provided as a Source Data file.



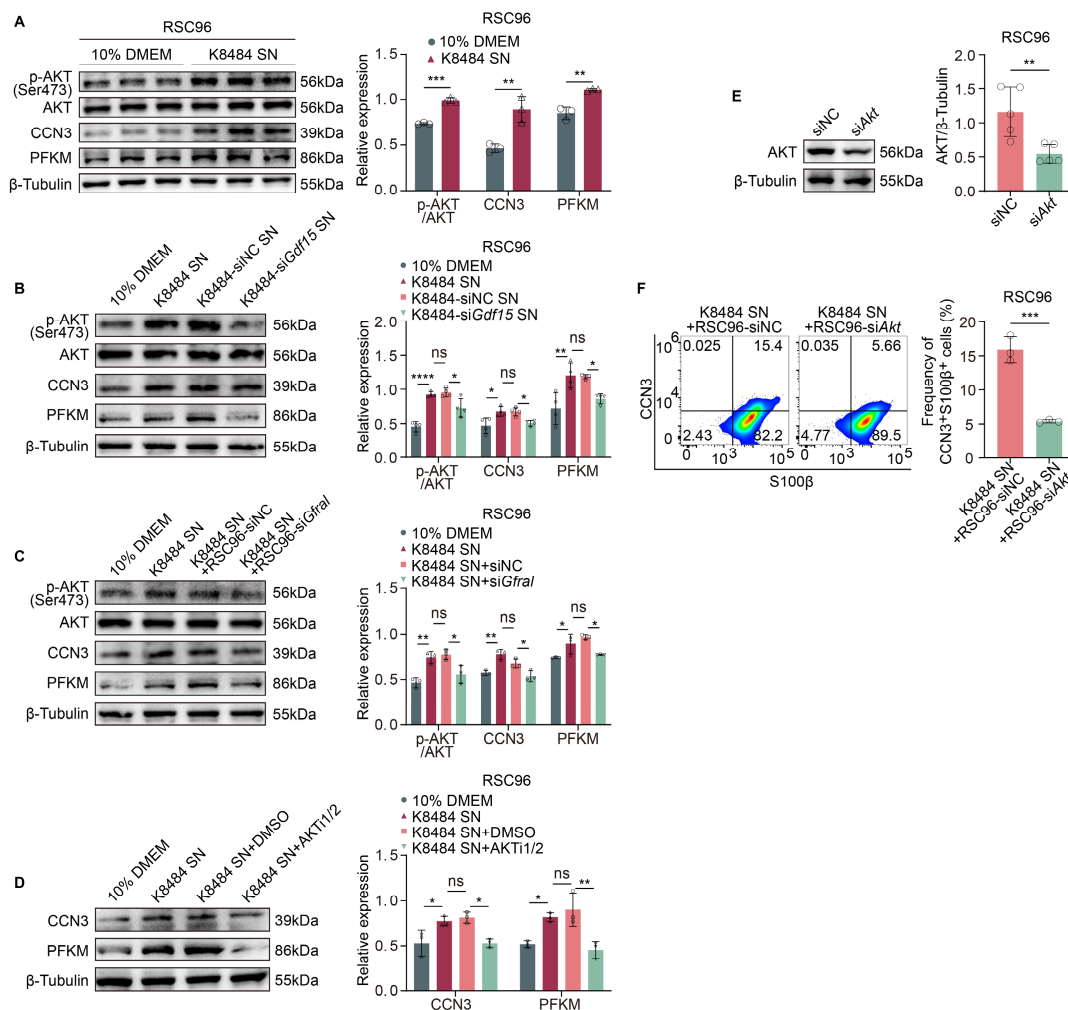
Supplementary Fig. 10 | PFKM inhibition reverses the increase in CCN3⁺ SCs quantity and the density of TRPV1⁺/CGRP⁺ fibers in PDAC mice. **A** The PFKM protein levels in RSC96 cells treated with siPfk or scrambled siRNA. unpaired t test. ** $P < 0.01$ vs. siNC group. $n = 5$ independent experiments per group. **B** Flow cytometry analysis showed the proportion of CCN3⁺S100β⁺ cells in RSC96 cells treated with siPfk or scrambled siRNA following the incubation of K8484 cell supernatant. unpaired t test. **** $P < 0.0001$ vs. siNC group. $n = 3$ independent experiments per group. The gating strategy is shown in Supplementary Fig. 15. **C, D** Representative staining and quantification showed that ML251 suppressed the increased colocalization of TRPV1 and PGP9.5 or CGRP and PGP9.5 induced by intratumoral injection of AAV-CNP-Gfral in pancreatic tumor of PDAC mice. Scale bars: 50 μm. one-way ANOVA with Tukey's post hoc test for multiple comparisons. Gfral+ML251 vs. Gfral+Saline: *** $P < 0.001$. $n = 5$ mice per group. **E, F** Representative staining and quantification showed that ML251 suppressed

the colocalization of TRPV1 and PGP9.5 or CGRP and PGP9.5 in pancreatic tumor of PDAC mice. Scale bars: 50 μ m. one-way ANOVA with Tukey's post hoc test for multiple comparisons. ML251 vs. Saline: *** $P < 0.001$, **** $P < 0.0001$. $n = 5$ mice per group. Data are shown as the mean $\pm$ SEM. ns, not significant, ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$. Source data are provided as a Source Data file.



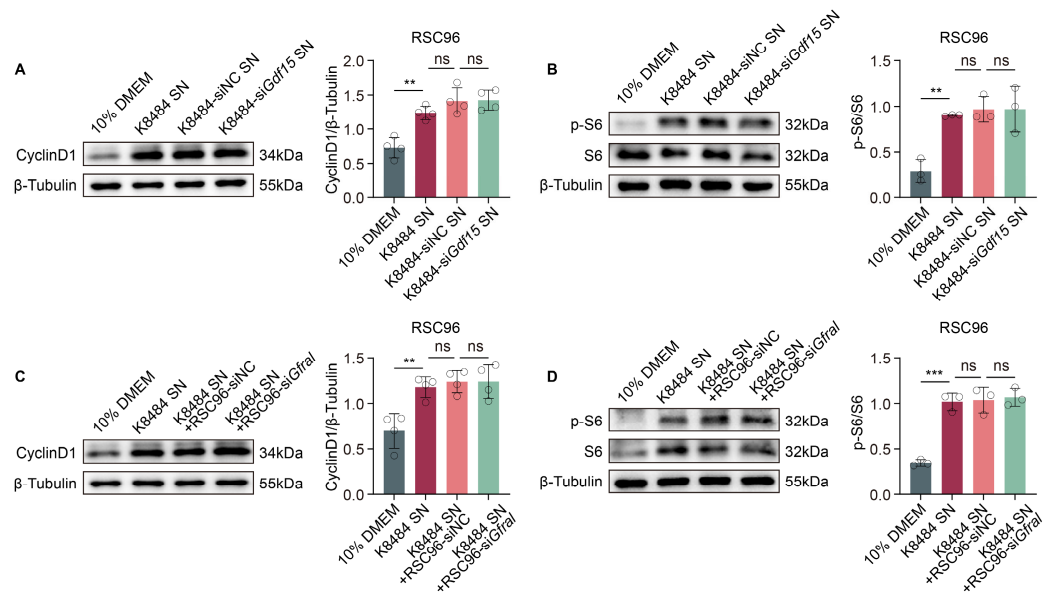
Supplementary Fig. 11 | GFRAL-mediated upregulation of PFKM in SCs is essential for PDAC pain. **A** Specimen diagrams and quantification showing the pancreatic tumor of mice following the intratumoral co-injection of AAV-CNP-*Gfral* and AAV-CNP-sh*PfkM*. Scale bars: 1 cm. unpaired t test. *** $P < 0.001$ vs. shNC group. $n = 5$ mice per group. **B-C** Mechanical allodynia and movement restriction in PDAC mice were explored following intratumoral co-injection of AAV-CNP-*Gfral* and AAV-CNP-sh*PfkM*. **(B)** two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: ** $P < 0.01$, *** $P < 0.001$, **** $P < 0.0001$ vs. shNC group. $n = 5$ mice per group. **(C)** unpaired t test. ** $P < 0.01$ vs. shNC group. $n = 5$ mice per group. **D** Specimen diagrams and quantification showing the pancreatic tumor of mice following the intratumoral injection of AAV-CNP-sh*PfkM*. Scale bars: 1 cm. unpaired t test. ** $P < 0.01$ vs. shNC group. $n = 5$ mice per group. **E-F** Mechanical allodynia and movement restriction in PDAC mice were explored following intratumoral injection of AAV-CNP-sh*PfkM*. **(E)** two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: * $P < 0.05$, ** $P < 0.01$, **** $P < 0.0001$ vs. shNC group. $n = 5$ mice per group. **(F)** unpaired t test. **** $P < 0.0001$ vs. shNC group. $n = 5$ mice per group. **G** Mechanical allodynia in PDAC mice following intratumoral injection of AAV-CNP-sh*PfkM* or AAV-CNP-scrambled shRNA at week 5. two-way repeated measures ANOVA. Šidák's

post hoc test for multiple comparisons: $**P < 0.01$, $****P < 0.0001$ vs. shNC group. $n = 5$ mice per group. **H** The mRNA levels of neurotrophic factors (*Ngf*, *Bdnf*, *Gdnf*, *Igfbp5*, *Btc*, *Crlf1*, *Artn*, *Ntf3*) in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant. unpaired t test. $*P < 0.05$, $**P < 0.01$ vs. shNC group. $n = 5$ independent experiments per group. **I** ELISA analysis reveals the secretion levels of NGF, BDNF, and IGFBP5 in conditioned medium from the co-culture of K8484 cells and RSC96 cells. unpaired t test. $*P < 0.05$, $***P < 0.001$, $****P < 0.0001$, vs. RSC96+RSC96 CM group. $n = 3$ independent experiments per group. Data are shown as the mean $\pm$ SEM. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$. Source data are provided as a Source Data file.

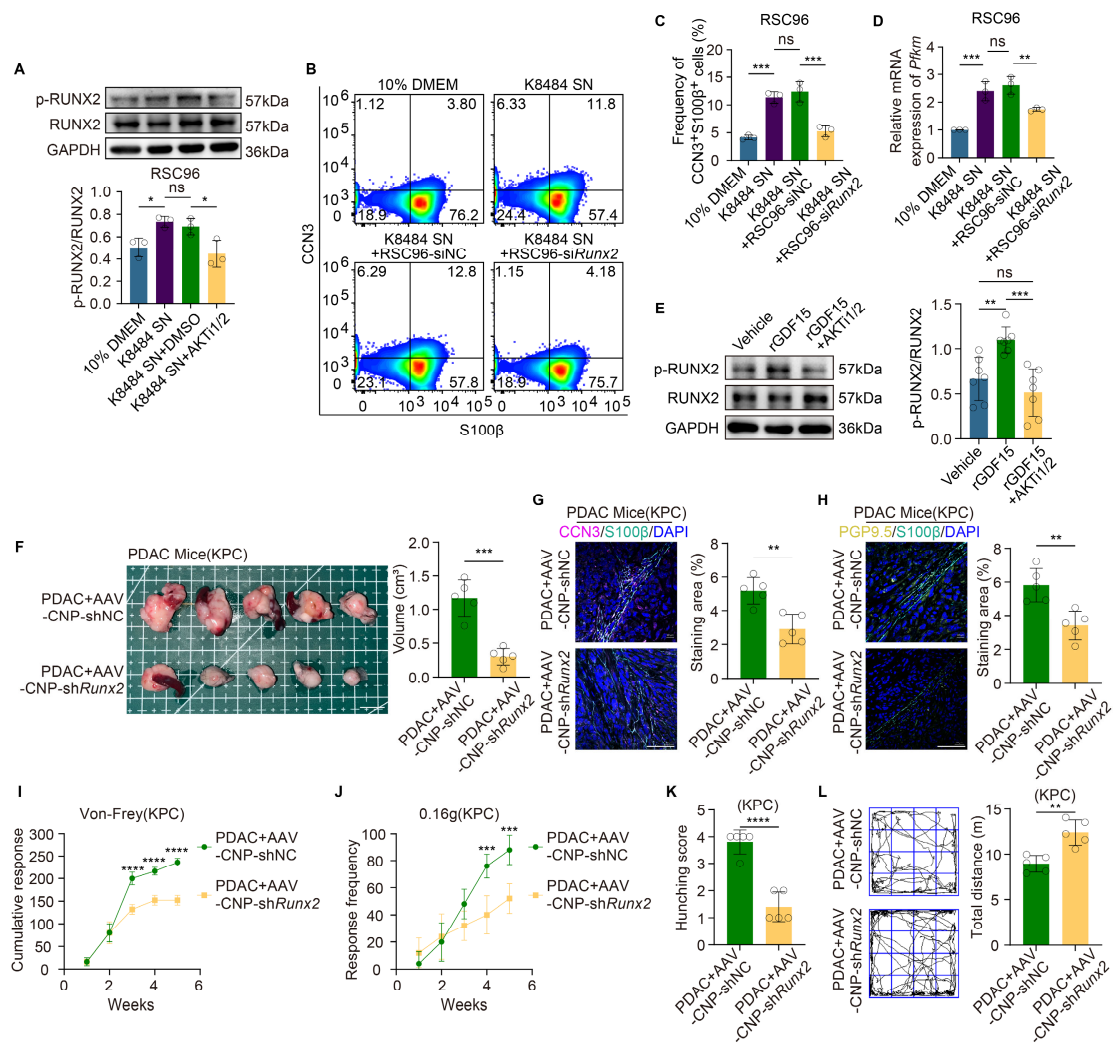


Supplementary Fig. 12 | GDF15-GFRAL drives CCN3⁺ Schwann cell proliferation via AKT pathway activation. **A** Representative immunoblot images showed the protein level of p-AKT, PFKM and CCN3 in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant. unpaired t test. $^{**}P < 0.01$, $^{***}P < 0.001$ vs. 10% DMEM group. $n = 3$ independent experiments per group. **B** Representative immunoblot images showed the protein level of p-AKT, PFKM and CCN3 in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant treated with siGdf15 or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{****}P < 0.0001$ vs. siNC group. $n = 4$ independent experiments per group. **C** Representative immunoblot images showed the protein level of p-AKT, PFKM and CCN3 in RSC96 cells were examined following the incubation of 10%DMEM or K8484 cell supernatant treated with siGfral or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. $^{*}P < 0.05$, $^{**}P < 0.01$ vs. siNC group. $n = 3$ independent experiments per group. **D** Representative immunoblot images showed the protein level of PFKM and CCN3 were

explored in RSC96 cells treated with AKTi1/2 following the incubation of K8484 cell supernatant. one-way ANOVA with Tukey's post hoc test for multiple comparisons. $*P < 0.05$, $**P < 0.01$ vs. siNC group. $n = 3$ independent experiments per group. **E** The AKT protein levels in RSC96 cells treated with si*Akt* or scrambled siRNA. unpaired t test. $**P < 0.01$ vs. siNC group. $n = 5$ independent experiments per group. **F** Flow cytometry analysis showed the proportion of CCN3⁺S100β⁺ cells in RSC96 cells treated with si*Akt* or scrambled siRNA following the incubation of K8484 cell supernatant. unpaired t test. $***P < 0.001$ vs. siNC group. $n = 3$ independent experiments per group. The gating strategy is shown in Supplementary Fig. 15. Data are shown as the mean $\pm$ SEM. ns, not significant, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$. Source data are provided as a Source Data file.

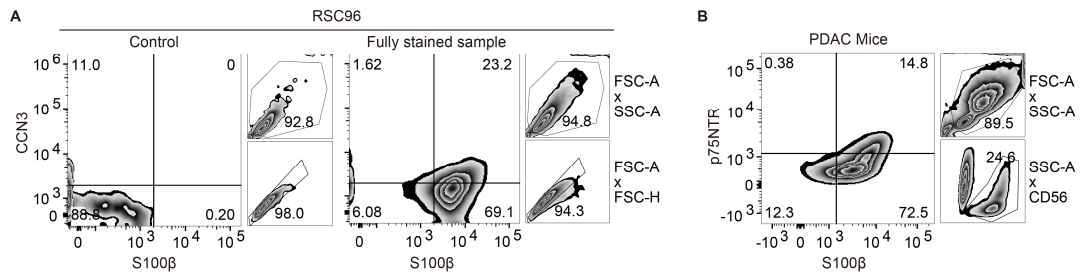


Supplementary Fig. 13 | GDF15-GFRAL does not affect proliferation pathways other than those mediated by PFKM. **A** Representative immunoblot images showed the protein level of CyclinD1 in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant treated with siGdf15 or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. Not significant vs. siNC group. $n = 4$ independent experiments per group. **B** Representative immunoblot images showed the protein level of p-S6 in RSC96 cells were examined following the incubation of 10%DMEM or K8484 cell supernatant treated with siGdf15 or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. Not significant vs. siNC group. $n = 3$ independent experiments per group. **C** Representative immunoblot images showed the protein level of CyclinD1 in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant treated with siGfral or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. Not significant vs. siNC group. $n = 4$ independent experiments per group. **D** Representative immunoblot images showed the protein level of p-S6 in RSC96 cells were examined following the incubation of 10%DMEM or K8484 cell supernatant treated with siGfral or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. Not significant vs. siNC group. $n = 3$ independent experiments per group. Data are shown as the mean $\pm$ SEM. ns, not significant, ** $P < 0.01$, *** $P < 0.001$. Source data are provided as a Source Data file.



Supplementary Fig. 14 | AKT-mediated RUNX2 phosphorylation stimulates CCN3⁺ SCs proliferation and promotes PDAC pain. **A** The protein level of the Runx2 phosphorylation in RSC96 cells were explored following the incubation of K8484 cell supernatant with AKTi1/2 or DMSO. one-way ANOVA with Tukey's post hoc test for multiple comparisons. * $P < 0.05$ vs. DMSO group. $n = 3$ independent experiments per group. **B**, **C** Flow cytometry analysis showed the proportion of CCN3⁺S100 β ⁺ cells in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant treated with siRunx2 or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. *** $P < 0.001$ vs. DMSO group. $n = 3$ independent experiments per group. The gating strategy is shown in Supplementary Fig. 15. **D** The *Pfkf* mRNA level in RSC96 cells following the incubation of 10%DMEM or K8484 cell supernatant treated with siRunx2 or scrambled siRNA. one-way ANOVA with Tukey's post hoc test for multiple comparisons. ** $P < 0.01$ vs. DMSO group. $n = 3$ independent experiments per group. **E** The protein level of the Runx2

phosphorylation in RSC96 cells were explored following the incubation of K8484 cell supernatant with recombinant GDF15 and AKTi1/2. one-way ANOVA with Tukey's post hoc test for multiple comparisons. recombinant GDF15 vs. Vehicle: $**P < 0.01$, recombinant GDF15+AKTi1/2 vs. recombinant GDF15: $***P < 0.001$. $n = 7$ independent experiments per group. **F** The syngeneic KPC PDAC cancer cells were injected into the pancreas in situ. Specimen diagrams and quantification showing the KPC pancreatic tumor of mice following the intratumoral injection of AAV-CNP-sh*Runx2* or AAV-CNP-scrambled shRNA. Scale bars: 1 cm. unpaired t test. $***P < 0.001$ vs. shNC group. $n = 5$ mice per group. **G** Representative staining and quantification showed that intratumoral injection of AAV-CNP-sh*Runx2* inhibited the increased colocalization of CCN3 and S100 β in pancreatic tumor of KPC PDAC mice. Scale bars: 50 μ m. unpaired t test. $**P < 0.01$ vs. shNC group. $n = 5$ mice per group. **H** Representative immunofluorescence staining and quantification showed that inhibition of RUNX2 by using AAV-CNP-sh*Runx2* prevented the increased co-expression of the PGP9.5 and S100 β in pancreatic tumor of KPC PDAC mice. Scale bars: 50 μ m. unpaired t test. $**P < 0.01$ vs. shNC group. $n = 5$ mice per group. **I-L** Mechanical allodynia, spontaneous pain and movement restriction in KPC PDAC mice after intratumoral injection of AAV-CNP-sh*Runx2* or AAV-CNP-scrambled shRNA. (**I, J**) two-way repeated measures ANOVA. Šidák's post hoc test for multiple comparisons: $***P < 0.001$, $****P < 0.0001$ vs. shNC group. $n = 5$ mice per group. (**K**) Mann-Whitney U test. $***P < 0.001$ vs. Sham group. $n = 5$ mice per group. (**L**) unpaired t test. $**P < 0.01$ vs. shNC group. $n = 5$ mice per group. Data are shown as the mean $\pm$ SEM. ns, not significant, $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$. Source data are provided as a Source Data file.



Supplementary Fig. 15 | Representative sequential gating strategy for flow cytometry. A Representative sequential gating strategy used to identify CCN3⁺ SCs, starting by selecting the main intact cell population from the collected cells (FSC-A/SSC-A), then isolating non-aggregated single cells (FSC-A/FSC-H), and finally identifying the target cell populations (S100 β ⁺CCN3⁺ for CCN3⁺ SCs) from among these. This gating strategy corresponds to the flow cytometry data shown in Fig. 2A, 4A, 5A, 6K, and Supplementary Fig. 10B, 12F, 14B, 14C. **B** Representative sequential gating strategy used to identify SCs in PDAC tumor tissues, beginning with selection of the main intact cell population (FSC-A/SSC-A), progressing to isolation of non-aggregated single cells (FSC-A/FSC-H), then to gating of the broad SC population (CD56⁺ cells), and culminating in identification of the target cell populations (S100 β ⁺p75NTR⁺ for SCs). This gating strategy corresponds to the flow cytometry data shown in Supplementary Fig. 5G, 5H.

ID	VAS	NRS	Group	GDF15(ng/ml)	Sex	T	N	M	Smoking	Drinking	History
1	8.137	8	Pain	9.5219348	Female	T4	N2	M0	0	0	0
2	8.429	8	Pain	8.3219886	Female	T4	N2	M1	0	0	0
3	7.586	7	Pain	9.3426175	Female	T3	N1	M0	0	0	0
4	7.293	7	Pain	9.7258139	Male	T3	N0	M0	0	0	0
5	7.648	7	Pain	7.8532916	Male	T4	N2	M1	0	1	0
6	7.175	7	Pain	8.3948726	Male	T3	N0	M0	0	0	0
7	7.914	7	Pain	8.7022667	Female	T3	N1	M0	0	0	0
8	7.362	7	Pain	10.315075	Male	T3	N0	M0	0	0	0
9	7.853	7	Pain	9.6400956	Male	T4	N2	M1	0	0	0
10	7.194	7	Pain	10.761148	Male	T3	N0	M0	0	0	0
11	6.715	6	Pain	7.1745829	Male	T2	N1	M0	0	0	0
12	6.328	6	Pain	7.5923714	Male	T4	N1	M1	1	0	0
13	6.847	6	Pain	7.4857132	Female	T2	N0	M0	0	0	0
14	6.139	6	Pain	6.9229354	Male	T2	N1	M1	0	0	1
15	6.526	6	Pain	8.3320356	Male	T4	N1	M1	0	0	1
16	6.902	6	Pain	6.9320574	Female	T2	N0	M0	0	0	0
17	5.371	5	Pain	6.8394176	Female	T4	N1	M1	0	0	0
18	5.864	5	Pain	6.2938465	Female	T3	N0	M0	0	0	0
19	5.239	5	Pain	5.5182946	Female	T2	N0	M0	0	0	0
20	5.756	5	Pain	5.5293846	Male	T1	N0	M0	1	0	1
21	5.182	5	Pain	12.456346	Female	T4	N1	M1	0	0	0
22	5.943	5	Pain	5.6806839	Female	T3	N0	M0	0	0	0
23	5.617	5	Pain	7.299137	Female	T2	N0	M0	1	0	0
24	5.498	5	Pain	7.7460061	Male	T1	N0	M0	1	1	1
25	4.126	4	Pain	6.6712539	Male	T3	N1	M1	0	0	0
26	4.895	4	Pain	5.8591742	Female	T0	N2	M1	0	1	0
27	4.318	4	Pain	5.381527	Female	T2	N0	M0	1	0	1
28	4.754	4	Pain	6.2691439	Male	T0	N2	M0	0	0	0
29	4.169	4	Pain	5.9215486	Male	T4	N1	M1	0	0	0
30	4.837	4	Pain	4.7954133	Female	T4	N1	M0	0	0	0
31	4.592	4	Pain	4.7285392	Female	T3	N0	M0	0	0	0
32	4.283	4	Pain	7.0854267	Male	T3	N1	M1	0	0	0
33	4.716	4	Pain	4.9441854	Female	T0	N2	M1	0	1	0
34	4.948	4	Pain	4.658761	Female	T2	N0	M0	0	0	1
35	4.305	4	Pain	8.7616065	Male	T0	N2	M1	0	0	0
36	4.472	4	Pain	4.6925785	Male	T4	N1	M1	0	0	0
37	4.829	4	Pain	3.6443111	Female	T4	N1	M0	0	0	0
38	4.164	4	Pain	6.4558158	Female	T3	N0	M0	0	0	0
39	3.257	3	Pain	4.2174095	Female	T3	N1	M1	0	0	0
40	3.819	3	Pain	5.5713287	Female	T4	N1	M1	0	0	0
41	3.435	3	Pain	5.1678943	Female	T3	N1	M1	0	0	1
42	3.976	3	Pain	3.8435292	Male	T4	N2	M0	1	0	0

43	3.582	3	Pain	4.9283576	Female	T0	N0	M1	0	0	1
44	3.149	3	Pain	5.5729381	Male	T2	N0	M0	0	0	0
45	3.763	3	Pain	3.4129785	Female	T3	N1	M1	0	0	0
46	3.294	3	Pain	5.8396173	Female	T4	N1	M1	0	0	0
47	3.618	3	Pain	4.4987153	Male	T4	N2	M0	1	1	0
48	3.827	3	Pain	5.6592817	Female	T2	N1	M0	0	0	0
49	3.491	3	Pain	4.7283942	Male	T2	N0	M0	0	0	0
50	3.936	3	Pain	4.8392746	Male	T4	N0	M0	0	0	0
51	3.154	3	Pain	3.1021009	Female	T3	N1	M0	0	0	0
52	3.728	3	Pain	4.6443111	Female	T4	N1	M1	0	0	0
53	3.365	3	Pain	4.3086694	Female	T3	N1	M1	0	0	1
54	3.892	3	Pain	2.9744023	Male	T4	N2	M0	0	0	0
55	3.547	3	Pain	4.1761121	Female	T0	N0	M1	0	0	0
56	3.219	3	Pain	4.1196553	Male	T2	N0	M0	0	0	0
57	3.874	3	Pain	6.9914907	Female	T3	N1	M1	0	0	0
58	3.536	3	Pain	4.2178996	Female	T4	N1	M1	0	0	0
59	3.982	3	Pain	3.1510828	Male	T4	N2	M0	1	1	0
60	3.417	3	Pain	4.1522513	Female	T2	N1	M0	0	0	0
61	3.768	3	Pain	5.9652955	Male	T2	N0	M0	0	0	0
62	3.293	3	Pain	5.5938923	Male	T4	N0	M0	0	0	0
63	2.147	2	Pain	3.3174986	Male	T1	N1	M1	0	0	0
64	2.859	2	Pain	4.2758146	Male	T4	N2	M0	0	0	0
65	2.634	2	Pain	4.8921547	Female	T3	N1	M0	1	1	1
66	2.978	2	Pain	3.8326175	Male	T2	N0	M0	0	0	0
67	2.315	2	Pain	3.8641395	Male	T4	N0	M0	0	0	0
68	2.746	2	Pain	5.2795486	Female	T2	N0	M0	0	0	0
69	2.593	2	Pain	3.4928375	Female	T2	N0	M0	0	0	0
70	2.817	2	Pain	4.5982945	Male	T1	N1	M1	0	0	0
71	2.462	2	Pain	3.600233	Male	T4	N2	M1	0	0	0
72	2.938	2	Pain	4.3753809	Female	T3	N1	M0	1	1	1
73	2.176	2	Pain	5.6039442	Male	T2	N0	M0	0	0	0
74	2.694	2	Pain	2.4280536	Male	T4	N0	M1	0	0	0
75	2.351	2	Pain	4.0621357	Female	T2	N0	M0	1	0	0
76	2.331	2	Pain	5.1703289	Female	T2	N0	M0	0	0	0
77	0	0	Con	1.3741395	Male	T3	N0	M0	0	0	0
78	0	0	Con	1.2168328	Male	T2	N3	M0	0	0	0
79	0	0	Con	2.1591873	Female	T0	N0	M0	0	0	1
80	0	0	Con	1.0795282	Female	T2	N0	M0	0	0	0
81	0	0	Con	1.2386295	Female	T2	N0	M0	0	0	0
82	0	0	Con	1.3395271	Female	T4	N0	M0	1	0	0
83	0	0	Con	1.5175295	Female	T2	N0	M0	0	1	0
84	0	0	Con	1.3291854	Male	T3	N0	M0	0	0	0
85	0	0	Con	2.2276184	Female	T2	N0	M0	0	0	0

86	0	0	Con	1.9846392	Female	T4	N0	M1	0	0	0
87	0	0	Con	1.3729583	Female	T3	N0	M0	0	0	1
88	0	0	Con	1.1397153	Female	T2	N0	M0	1	0	0
89	0	0	Con	2.6152684	Female	T1	N0	M0	0	0	1
90	0	0	Con	2.3489272	Female	T2	N0	M0	0	0	1
91	0	0	Con	0.9947385	Female	T3	N0	M0	0	0	0
92	0	0	Con	1.4592831	Female	T2	N0	M0	0	1	0
93	0	0	Con	1.2483917	Male	T2	N0	M0	0	0	0
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95	0	0	Con	1.5392746	Male	T1	N0	M0	0	0	0
96	0	0	Con	2.3652509	Male	T3	N0	M0	0	0	0
97	0	0	Con	4.2953617	Male	T2	N3	M0	0	0	0
98	0	0	Con	3.892129	Female	T0	N0	M0	0	0	1
99	0	0	Con	5.2054671	Female	T2	N0	M0	0	0	0
100	0	0	Con	2.2257611	Female	T2	N0	M0	0	0	0
101	0	0	Con	4.8780175	Female	T4	N0	M0	0	0	0
102	0	0	Con	2.47053	Female	T2	N0	M0	0	0	0
103	0	0	Con	4.7885923	Male	T3	N0	M0	0	0	0
104	0	0	Con	3.9144614	Female	T2	N0	M0	0	0	0
105	0	0	Con	3.8562264	Female	T4	N0	M1	0	0	0
106	0	0	Con	2.4605918	Female	T3	N0	M0	0	0	1
107	0	0	Con	2.0582675	Female	T2	N0	M0	0	0	1
108	0	0	Con	3.7340537	Female	T1	N0	M0	0	0	1
109	0	0	Con	3.9897945	Female	T2	N0	M0	0	0	0
110	0	0	Con	6.7337711	Female	T3	N0	M0	0	0	0
111	0	0	Con	3.3239743	Female	T2	N0	M0	0	0	0
112	0	0	Con	2.8719595	Male	T2	N0	M0	0	0	0
113	0	0	Con	2.1516054	Female	T0	N0	M0	0	0	0
114	0	0	Con	5.5725897	Male	T1	N0	M0	0	0	0
115	0	0	Con	3.7853679	Male	T3	N0	M0	0	0	1
116	0	0	Con	5.2265846	Male	T2	N0	M0	0	0	0
117	0	0	Con	6.4196345	Female	T0	N0	M0	0	0	0
118	0	0	Con	4.7817118	Female	T4	N1	M0	0	0	0
119	0	0	Con	4.4165275	Male	T3	N0	M0	1	0	0
120	0	0	Con	6.1295724	Female	T0	N0	M0	0	0	0

Supplementary Table 1 | Clinical characteristics of PDAC patients. Summary of clinical, and laboratory data for the 120 PDAC patients included in this study. VAS, visual analogue scale; NRS, numerical rating scale; Group, pain status (No-pain or Pain); GDF15, growth differentiation factor 15; Sex; T, tumor stage; N, lymph node status; M, metastasis status. Data are presented as individual values.

Gene	Forward primer	Reverse primer
GDF15-MUS	CTGGCAATGCCTGAACAACG	GGTCGGGACTTGGTTCTGAG
CCN3-MUS	AGTGCCCCAGTATATCACCGA	TGCGGTCACAGTAGAGACCA
CCN3-RAT	ATTGTCATGGTTCCAGAGGG	TTCGACTCCTACGGTAGCTT
GFRAL-RAT	GCACATGCTTCACAGCAAAT	CTCGGACGTGTGGTTGATAG
HK1-RAT	GGAAGGAGACCAACAGCAAA	GGCCTTTGATCCCCATGTAG
HK2-RAT	ACTCAATGACATCCGAACCG	GCTGAGTTTCCCTTGAACA
PFKM-RAT	GGCCTGTAGAGGTTTGAAG	CATACCTTGGGCATCTCCAC
PFKL-RAT	GCCCACCAGAAGGTGTCTAA	AGGTACGGAGATTTTCTACAATGG
PFKP-RAT	CTGTGTCGTGTCAGTCTGAGAG	TTGCCCTCAAACTCCTTCC
PKM-RAT	CGACAGACGTCCTCTTAGG	TGAGAGAAATTCAGCCGAGC
PFKM-PROMOTER-RAT	TTGCTGTGGATTGTAT	AGGCAGTGGGTGGTTA
TRPV1-RAT	CTGACGGCAAGGATGACTAC	CAGGGCAAAGTTCTTCCAGT
CGRP-RAT	AGGTGAGCCCTGAGGTTTC	TTCTGGGCAGTGACACTAGA
NGF-RAT	AGTGTCTGGGCCCAATAAAG	CCTGTACGCCGATCAAAAAC
BDNF-RAT	ATTGCGCCCGGGACT	GCCTTCATGCAACCGAAGTA
GDNF-RAT	GATCCAAGAGGCCGGTGT	TCATCTTAGAGTCCCGTCCG
IGFBP5-RAT	GGGTTTGCTCAACGAAAAG	GATCCTTCTTCACAGCCTCG
BTC-RAT	TGATGGACGAACAACTCCC	GCGATGTTTCCGAAGAGGAT
CRLF1-RAT	TCTATGGGTCGAAAAGGCG	GTTTCGGGTCTTGTGTGACT
ARTN-RAT	TGATCCATTTGAGCTTCGGG	GACAATGCAGTAGGCTCTCC
NTF3-RAT	GGTGGGCGAGACTGAATGAC	ATCCATGTTGTTGCCTTGAT

Supplementary Table 2 | Primer sequences used for qPCR. List of oligonucleotide primers used for qPCR in this study. The table includes gene name, forward primer sequence, reverse primer sequence and species.