Expanded View Figures

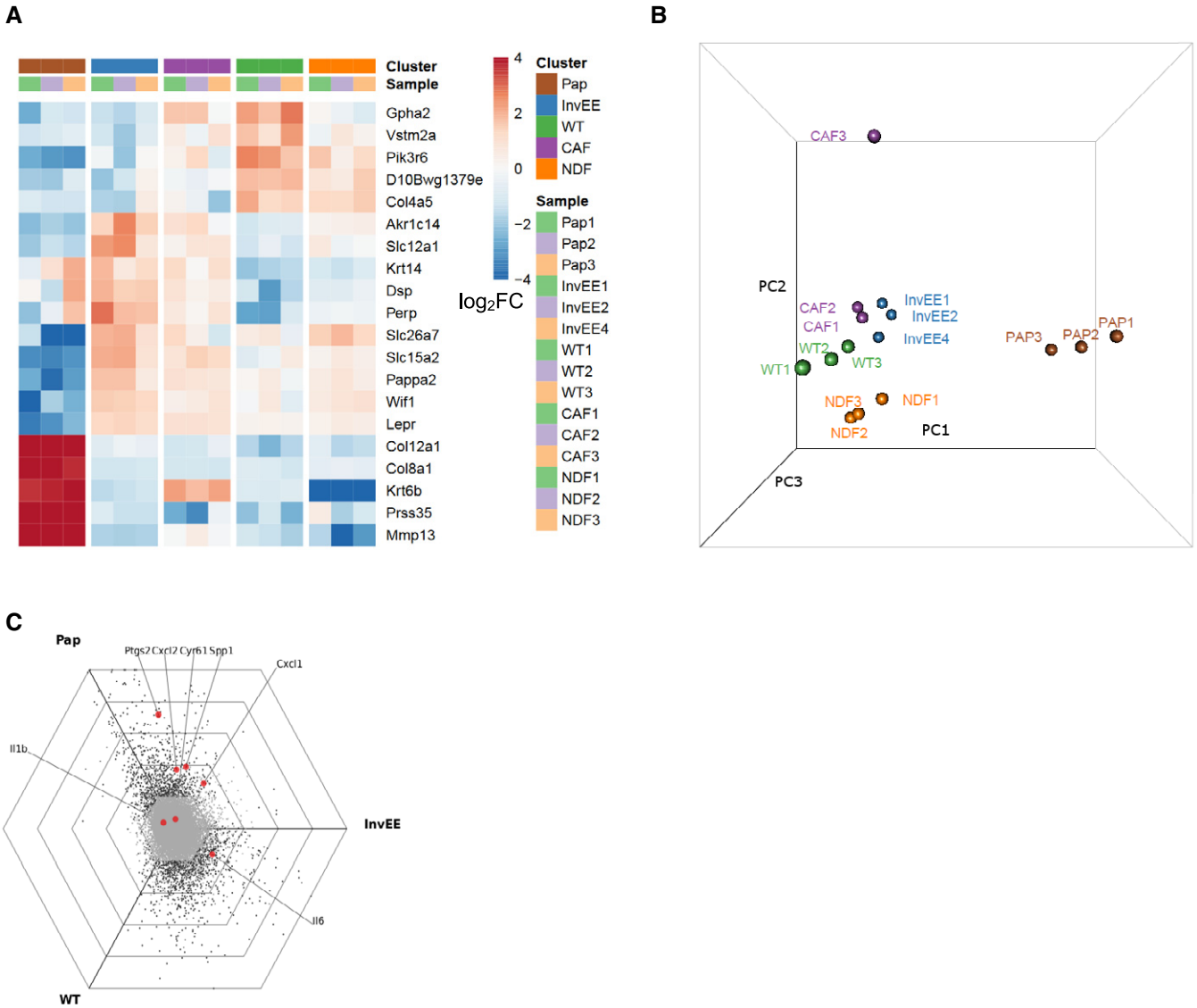

Figure EV1. Comparison of the InvEE CAF signature with the pro-inflammatory CAF signature characterized by Erez *et al* (2010).

A Combined clustering of our dataset (WT: normal skin, InvEE: inflammatory skin and Pap: wound-induced papillomas) and the dataset obtained by Erez *et al* (NDF: normal dermal fibroblasts and CAF: cancer-associated fibroblasts) based on global differential gene expression.

B Principle component analysis of our dataset and the dataset from Erez *et al* purple: CAF, orange: NDF, blue: InvEE, green: WT and brown: Pap).

C Hexagonal triwise plot showing the pro-inflammatory gene signature, determined by Erez *et al* and mapped on our gene expression analysis. (Ptgs2 = Cox2, SPP1 = Osteopontin, Cyr61 = CCN1).

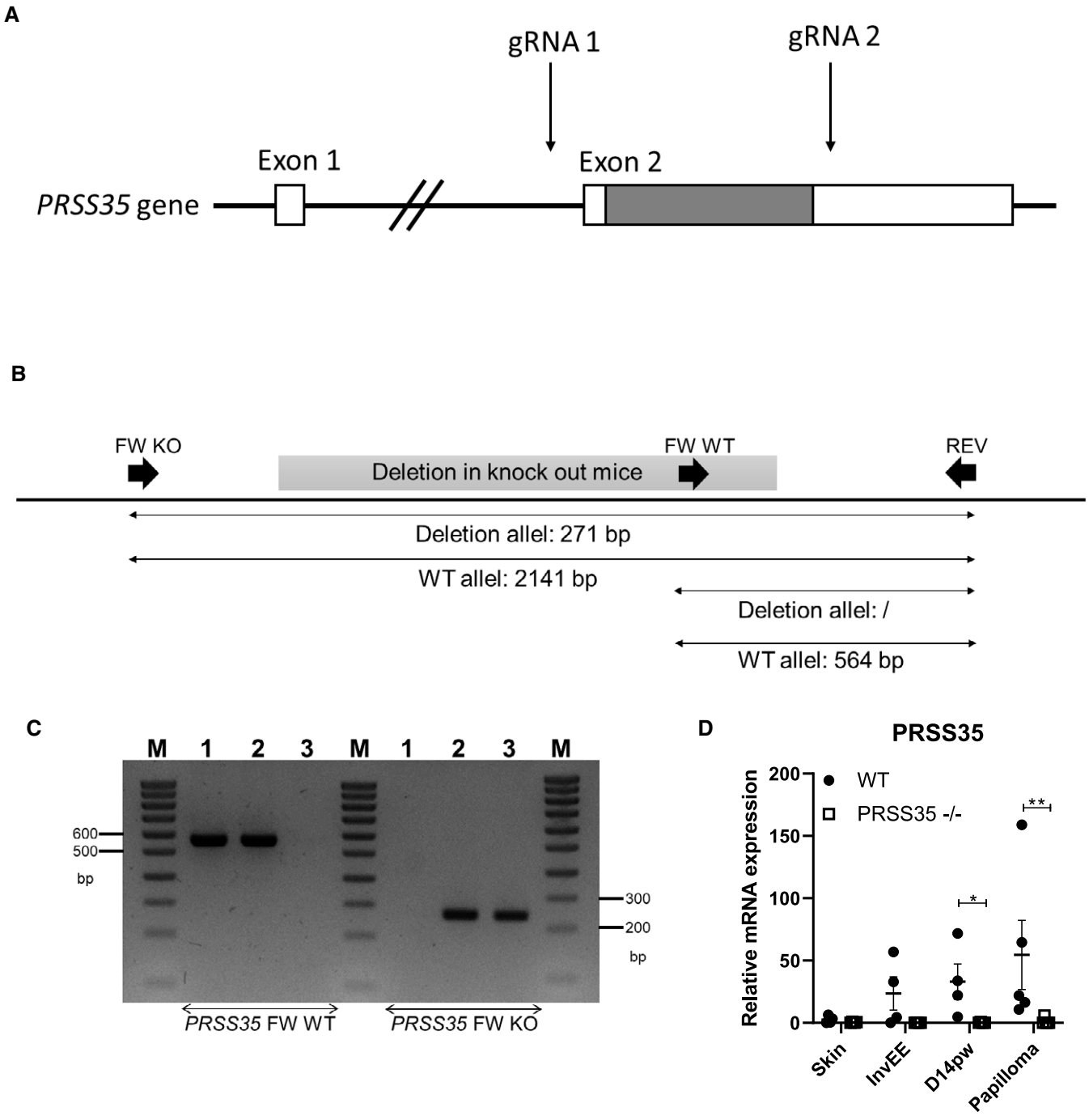

Figure EV2. Generation of PRSS35 knockout (B6J-Prss35em1Irc) mice.

A Positioning of CRISPR-Cas gRNAs on the *PRSS35* gene. The sequence between the two gRNAs was deleted upon cleavage by CRISPR-Cas9 at the site of the gRNAs. The coding region is shaded.

B Genotyping strategy for detection of the presence or absence of PRSS35. Schematic representation of the primer bindings sites used.

C An agarose gel image for PRSS35 genotyping. M: Ladder, 1-3: genomic DNA extracted from tails from a WT, PRSS35 heterozygous and PRSS35 KO mouse.

D Relative mRNA expression levels of PRSS35 in tissue isolated from WT and PRSS35$^{-/-}$ mice ($n \geq 4$ per condition; *$P < 0.05$, **$P < 0.01$; Mann–Whitney test).

Figure EV3. PRSS35 does not alter proliferation or inflammatory responses in fibroblasts.

A Cell proliferation assay on PRSS35 WT and PRSS35 KO primary fibroblasts, as measured through live cell imaging ($n = 3$ biological replicates per condition, ns, Wilcoxon matched-paired rank test). Data represent means ± SEM

B Scratch wound assay of PRSS35 WT and PRSS35 KO primary fibroblasts. Scratch width was measured over time with live cell imaging ($n = 3$ per condition, ns, Wilcoxon matched-paired rank test). Data represent means ± SEM

C, D Relative RNA expression of the indicated genes in primary fibroblast isolated from WT and PRSS35 KO mice, untreated or after 24 h stimulation with 10 ng/ml TGF-β ($n = 6$ per genotype) or 20 ng/ml IL-1β (WT, $n = 5$; PRSS35 KO, $n = 6$) (*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$; two-way ANOVA with multiple comparisons). Data represent means ± SEM.

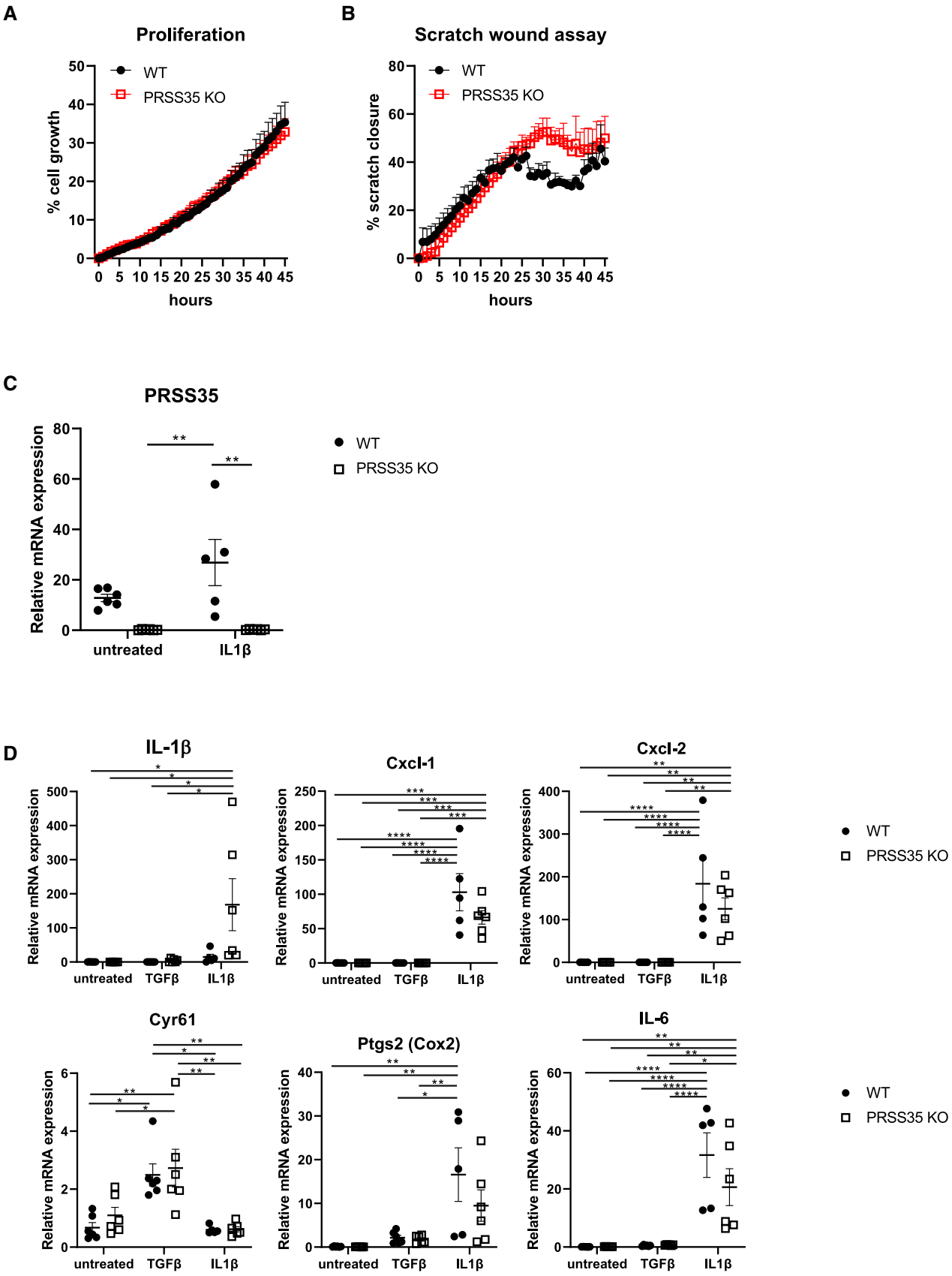
A
Proliferation
WT
PRSS35 KO
% cell growth
hours
B
Scratch wound assay
WT
PRSS35 KO
% scratch closure
hours
C
PRSS35
Relative mRNA expression
untreated
IL1β
WT
PRSS35 KO
D
IL-1β
Cxcl-1
Cxcl-2
Cyr61
Ptgs2 (Cox2)
IL-6
Relative mRNA expression
untreated
TGFβ
IL1β
WT
PRSS35 KO

Figure EV3.