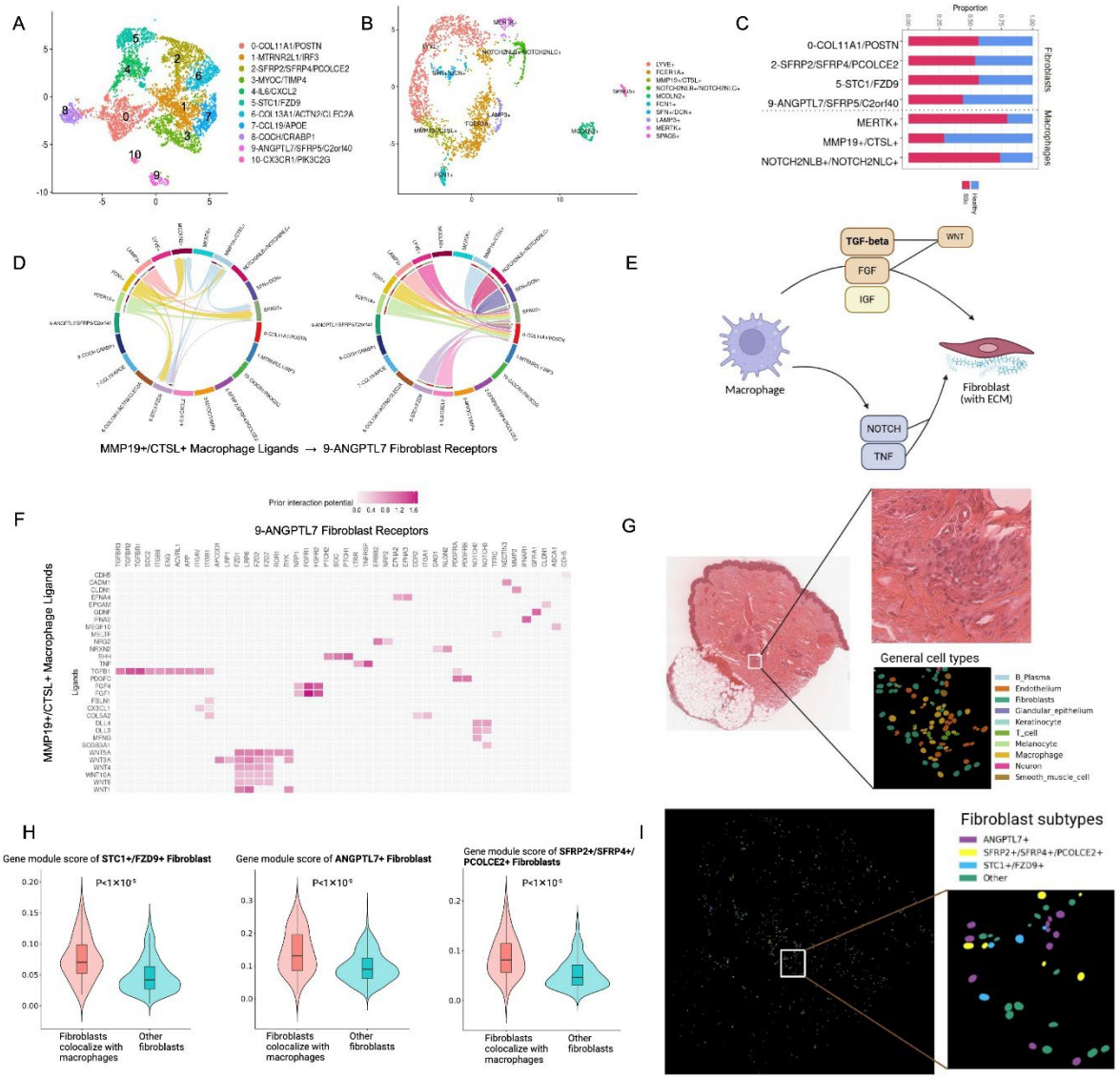

Figure 1. Skin single-cell analysis identifies pathogenic macrophage–fibroblast circuits in juvenile systemic sclerosis (jSSc).

(A) UMAP of 8,860 skin fibroblasts (4,893 jSSc and 4893 healthy) identifying 11 transcriptionally distinct subclusters by marker gene expression. **(B)** UMAP of 2,719 macrophages (852 jSSc and 1,867 healthy) identifying 10 annotated subclusters. **(C)** Bar plot of fibroblast and macrophage

subcluster proportions in jSSc vs. healthy samples. **(D)** CellChat analysis of *TGF-beta* ligand–receptor interactions between fibroblast and macrophage subtypes in jSSc (left) and healthy (right) skin, showing expanded intercluster connectivity in jSSc; numbered clusters denote fibroblasts, unnumbered denote macrophages. **(E)** Schematic of a macrophage-driven profibrotic circuit: macrophage-derived *TGF-beta*, *FGF*, and *IGF* activate fibroblast ECM programs via *WNT* signaling, while *NOTCH* and *TNF* reinforce chronic fibroblast activation. **(F)** NicheNet interaction heatmap highlighting signaling from *MMP19*+/*CTSL*+ macrophages to *ANGPTL7*+ fibroblasts via ligands (*TGFB1*, *AREG*, and *COL6A2*) and receptors (*TGFBR1*, *FGFR1*, and *FZD9I*). **(G)** Spatial transcriptomics showing macrophage-fibroblast colocalization (<25um) in jSSc skin; insets highlight high-resolution regions in the reticular dermis, perivascular infiltrate region. **(H)** Marker genes of *STC1*+/*FZD9*+, *ANGPTL7*+, and *SFRP2*+/*SFRP4*+ were significantly upregulated in the fibroblasts that colocalized with macrophages compared with non-colocalized fibroblasts ($p < 1 \times 10^{-5}$; using Wilcoxon rank sum test, Bonferroni-adjusted $p < 0.05$). **(I)** Spatial localization of *STC1*+/*FZD9*+, *ANGPTL7*+, and *SFRP2*+/*SFRP4*+ fibroblasts in the same biopsy region as shown in (G).