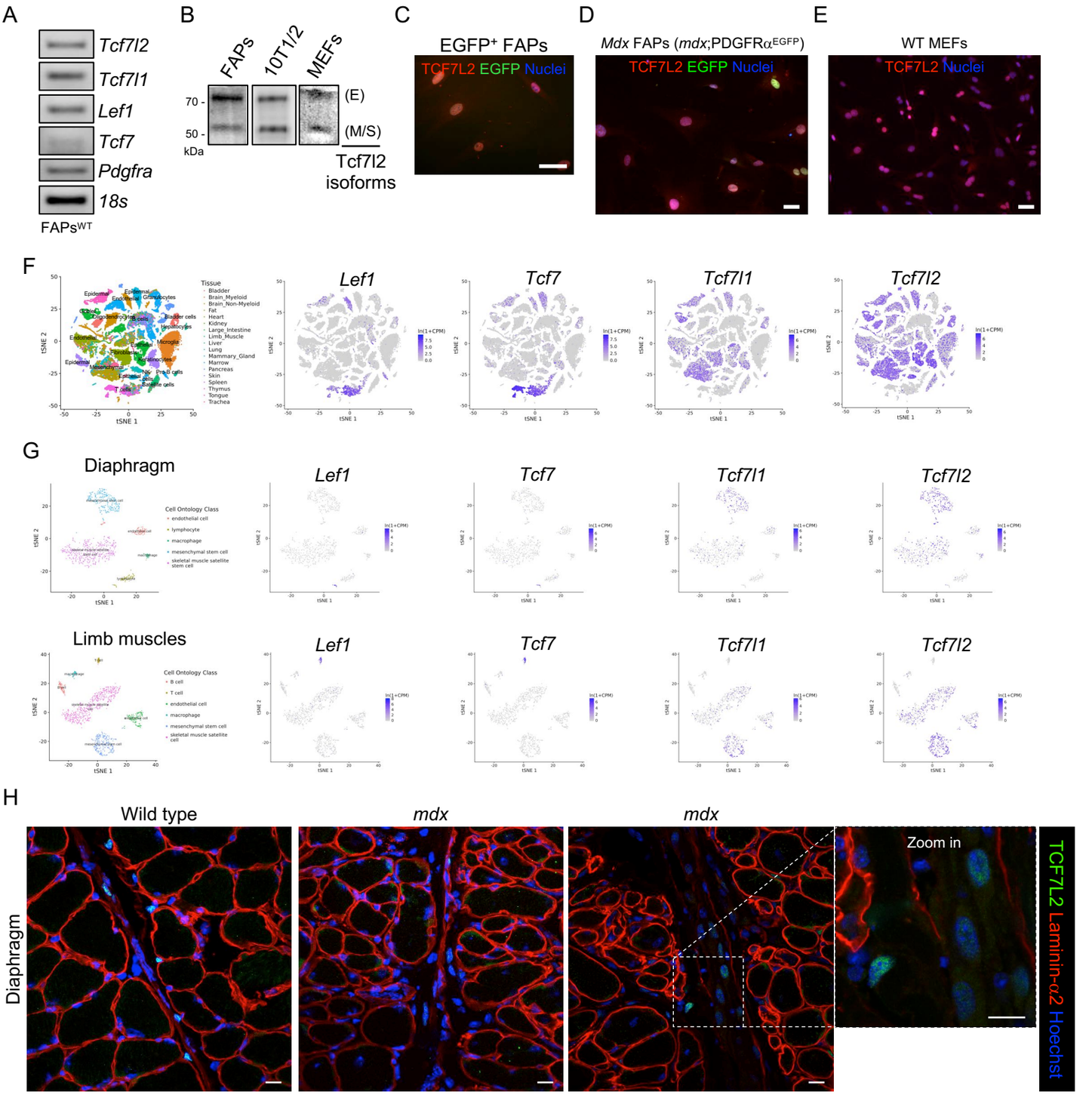

Fig. S1. Dynamic gene expression of Tcf/Lef in PDGFRα⁺ fibro-adipogenic progenitors and MSCs.

(A) Final gene expression product of Tcf/Lef was analyzed by RT-qPCR in a 2% agarose gel following 35 PCR cycles. The expression of *Pdgfra* was used as a positive control. (B) Representative western blot analysis showing TCF7L2 protein levels in muscle PDGFRa-EGFP⁺ FAPs, C3H 10T1/2 MSCs, and MEFs. (C-E) Immunofluorescence of TCF7L2 in FACS-isolated skeletal muscle PDGFRa-EGFP⁺ FAPs (C), PDGFRa-EGFP⁺ *mdx* FAPs (D), and cultured MEFs (E). Scale bar: 50 µm. TCF7L2 immunofluorescence (*red*) in MEFs. (F) A t-SNE plot of all cells collected by the microfluidic-droplet method, colored by the predominant cell type that composes each cluster. Cells were colored by cell type for diaphragm and limb muscles and visualized with t-SNE. t-SNE visualization of *Tcf/Lef* genes (from *grey*, low expression, to *blue*, high expression). (H) Z-stack confocal images showing the localization of TCF7L2⁺ cells in diaphragm muscle sections of adult wild-type and from the dystrophic *mdx* mice. Scale bars: 10 µm.

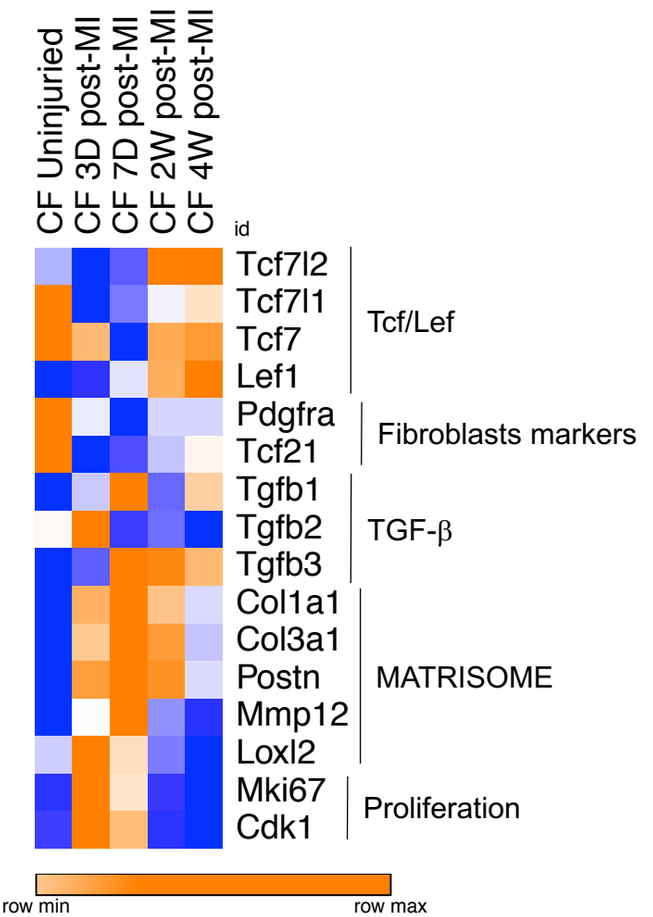

Fig. S2. Dynamics of Tcf/Lef gene expression in cardiac fibroblasts following myocardial infarction.

Heat map showing expression changes (RPKMs) of Tcf/Lef genes. Known fibroblasts markers, TGF-β ligands, matrix mediators (e.g. ECM genes), and proliferation-related genes are also shown. Each row is normalized to itself. Each column, per condition, represents the mean of three individual cardiac fibroblast samples (*n*=3).

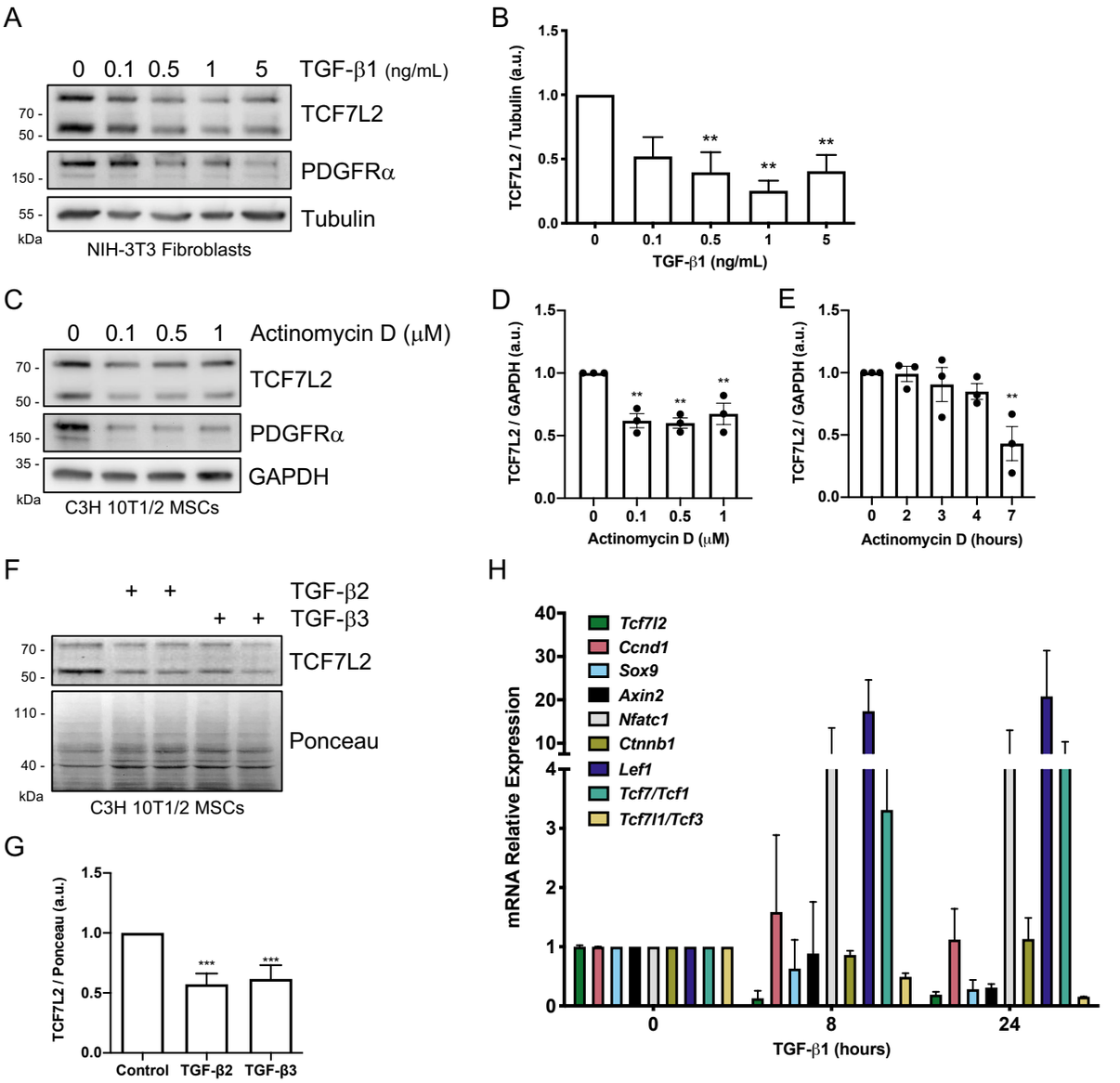

Fig. S3. Extracellular TGF-β ligands impair TCF7L2-mediated Wnt gene expression.

(A) Representative western blot analysis showing TCF7L2 and PDGFRα expression levels in NIH-3T3 fibroblasts after treatment with different concentrations of TGF-β1 for 24 h. GAPDH was used as the loading control. (B) Quantification of TCF7L2 protein expression. ***P*<0.005 by one-way ANOVA with Dunnett's post-test; *n*=4. (C) Representative western blot analysis showing TCF7L2 and PDGFRα levels in MSCs after treatment with different concentrations of actinomycin D for 7 h. GAPDH was used as the loading control. (D,E) Quantification of TCF7L2 protein expression. ***P*<0.005 by one-way ANOVA with Dunnett's post-test; *n*=3. (F) Representative western blot from three independent experiments, showing TCF7L2 protein levels after stimulation with TGF-β2 and TGF-β3 for 24 h (5 ng/ml) in MSCs. Ponceau was used as the loading control. (G) Quantification of TCF7L2 protein expression ****P*<0.001; One-Way ANOVA with Dunnett post-test; *n*=3. (H) *Tcf4* (*Tcf7l2*), *Ccnd1* (*CyclinD1*), *Sox9*, *Axin2*, *Nfatc1*, *Ctnnb1* (*β-catenin*), *Lef1*, *Tcf7* (*Tcf1*), and *Tcf7l1* (*Tcf3*) mRNA expression levels were analyzed by quantitative PCR in TGF-β1-treated C3H/10T1/2 MSCs at different time points (0, 8, 24 h). *n*=3.

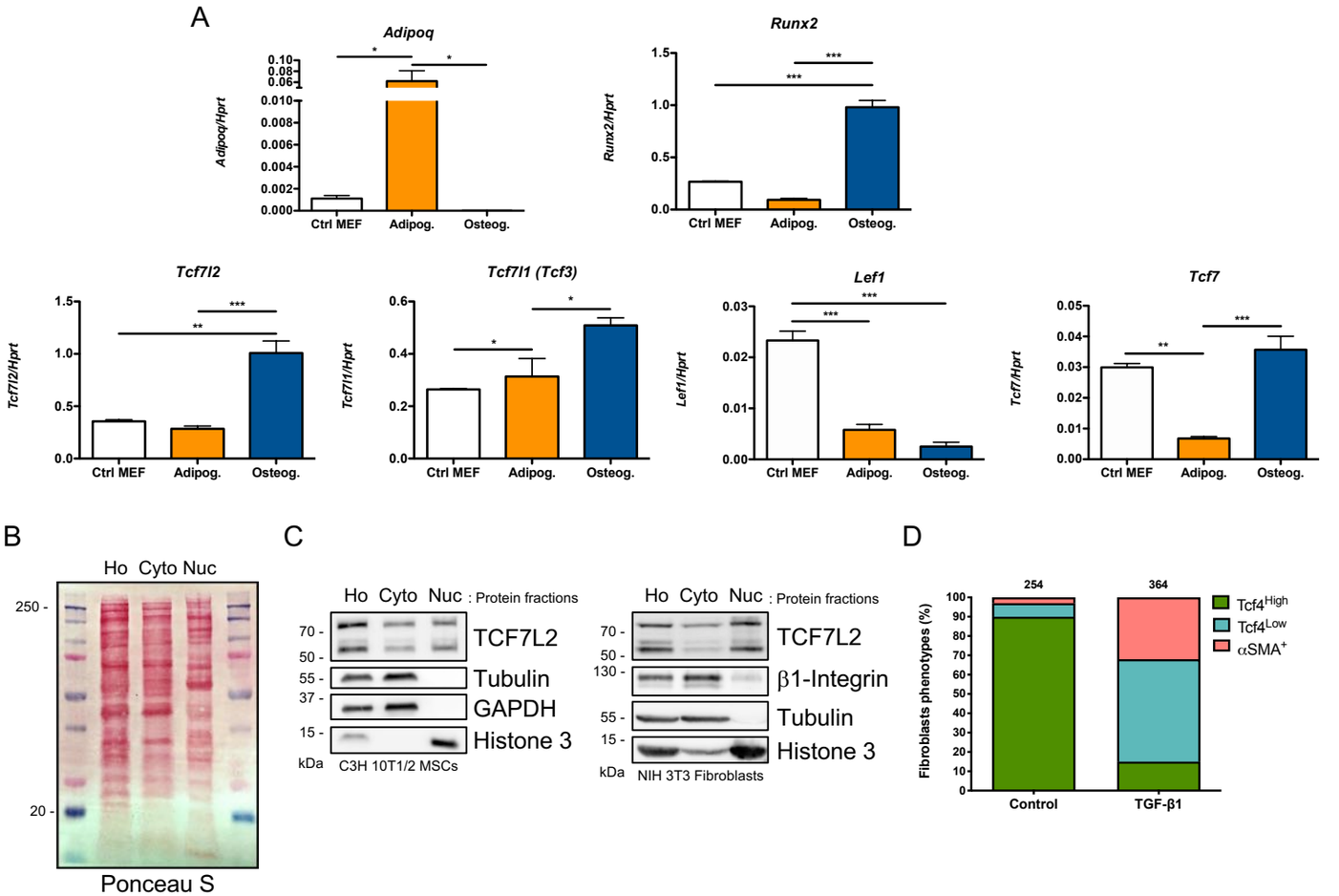

Fig. S4. Tcf/Lef gene expression varies in adipocytes and osteocytes.

(A) Adipoq, Runx2, Tcf7l2, Tcf7l1, Lef1, and Tcf7 mRNA expression levels were analyzed by digital droplet RT-qPCR in MEFs control (Ctrl MEF), MEFs-derived adipocytes (Adipog.: adipogenic cell medium), and MEFs-derived osteocytes (Osteog.: osteogenic cell medium). (B) Representative ponceau red staining of Ho: Whole cell lysate; Cyto: Cytoplasmic lysate; Nuc: Nuclei lysate. (C) Representative western blot analysis showing TCF7L2, Tubulin, GAPDH, Histone 3, and β1-Integrin protein levels in proliferating C3H/10T1/2 MSCs and NIH-3T3 fibroblasts. (D) Quantification of TCF7L2 fluorescence intensity in control- and TGF-β1-treated fibroblasts. TCF7L2^{Hi} (Tcf4^{Hi}), TCFL2^{low} (Tcf4^{low}), and αSMA+-phenotypes were quantified in control and TGF-β1-stimulated C3H/10T1/2 MPCs at 36 h. The numbers above each graph show the total quantified number of cells. n=3.

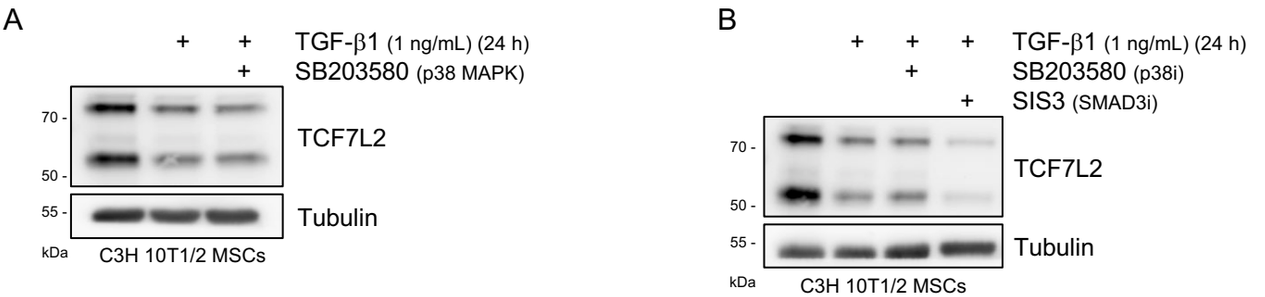

Fig. S5. Pharmacological Smad3 inhibition with SIS3 pronounces TGF-β-mediated downregulation of TCF7L2.

(A) Representative western blot analysis showing TCF7L2 expression levels in C3H/10T1/2 cells after TGF-β1 treatment (1 ng/ml) for 24 h. SB203580 (p38 MAPK inhibitor) was co-incubated with TGF-β1 for 24 h. Tubulin was used as the loading control. (B) Representative western blot analysis showing TCF7L2 expression levels in C3H 10T1/2 cells after TGF-β1 treatment (1 ng/ml) for 24 h. SB203580 (p38 MAPK inhibitor) or SIS3 (Smad3 inhibitor) were co-incubated with TGF-β1 for 24 h. Tubulin was used as the loading control.

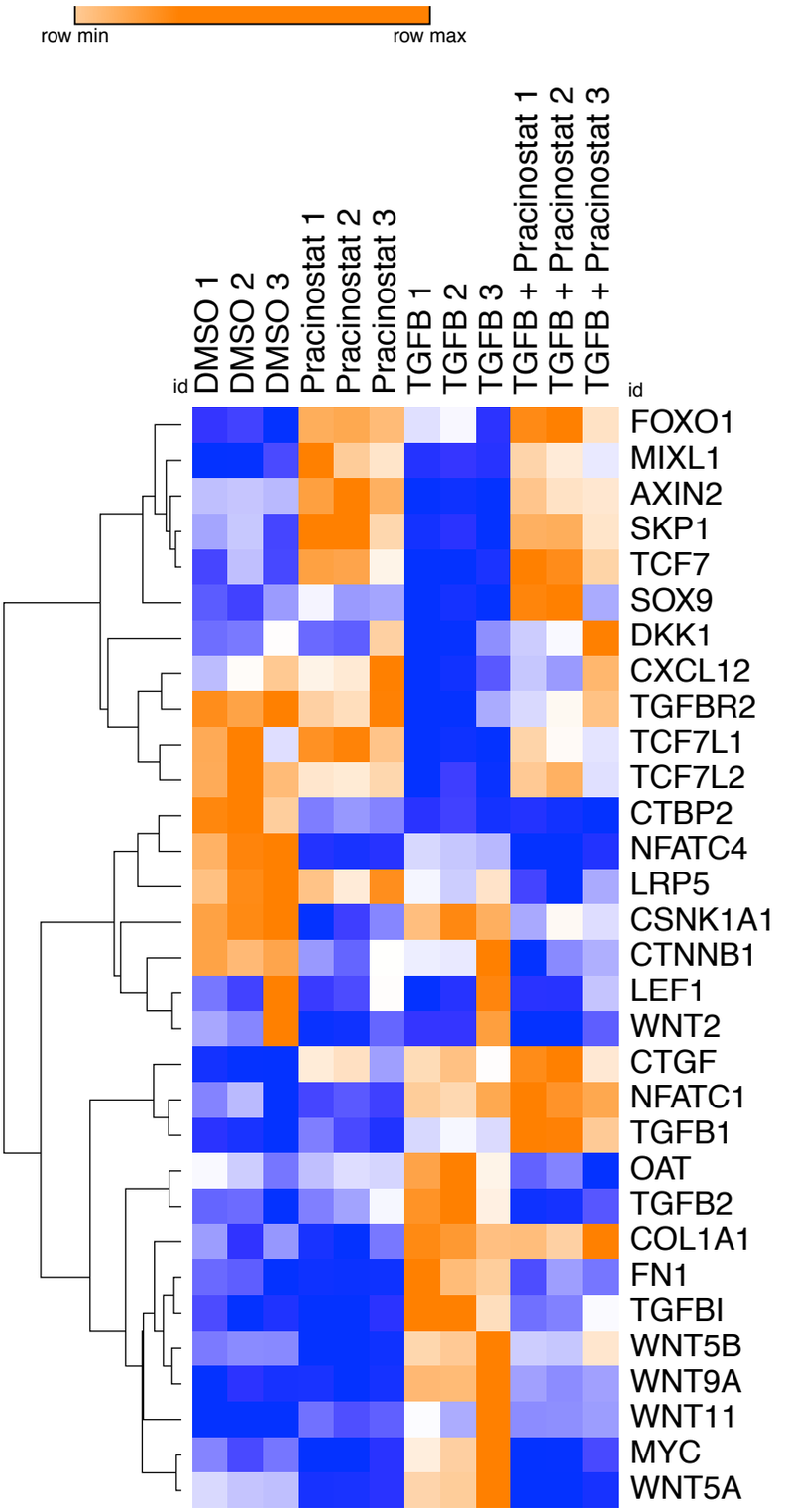

Fig. S6. TGF-β signaling impairs TCF7L2-mediated target gene expression and Wnt signaling via HDACs.

Heat map showing expression changes of several validated TCF7L2-downstream genes that are significantly repressed or increased by TGF-β and decreased by the pan HDAC inhibitor pracinostat. Each column, per treatment condition, represents an individual IPF lung fibroblast donor (n=3).

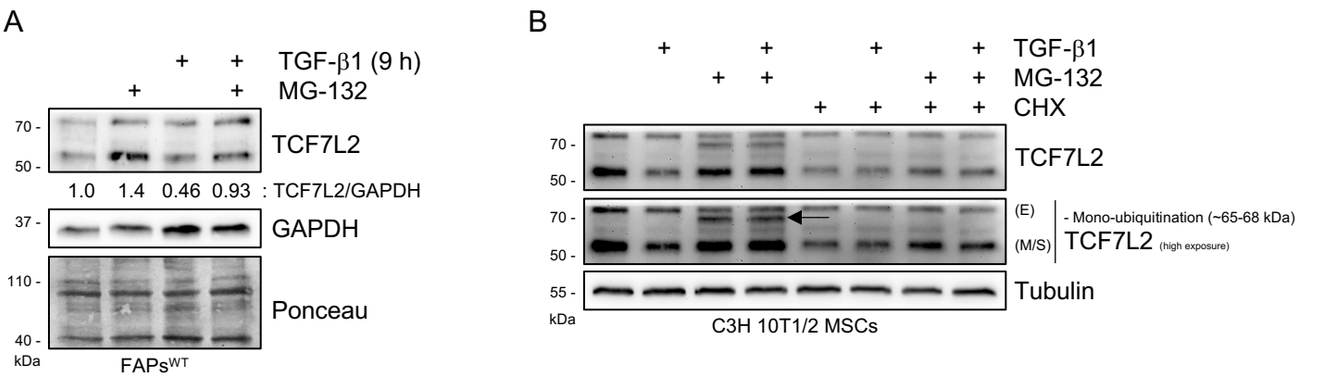

Fig. S7. Evaluation of the participation of the ubiquitin-proteasome system via MG132 inhibitor on the regulation of TCF7L2 protein expression.

(A) Representative western blot analysis showing TCF7L2 expression levels in C3H 10T1/2 cells after TGF-β1 treatment (5 ng/ml) for 9 h. MG132 (26S subunit proteasome inhibitor) was incubated alone or co-incubated with TGF-β1 for 9 h. GAPDH and ponceau red were used as the loading control. (B) Representative western blot analysis showing TCF7L2 expression levels in C3H 10T1/2 cells after TGF-β1 treatment (5 ng/ml) for 9 h. MG132 (26S subunit proteasome inhibitor) or cycloheximide (protein translation inhibitor) were incubated alone or co-incubated with TGF-β1 for 9 h. Tubulin was used as the loading control.

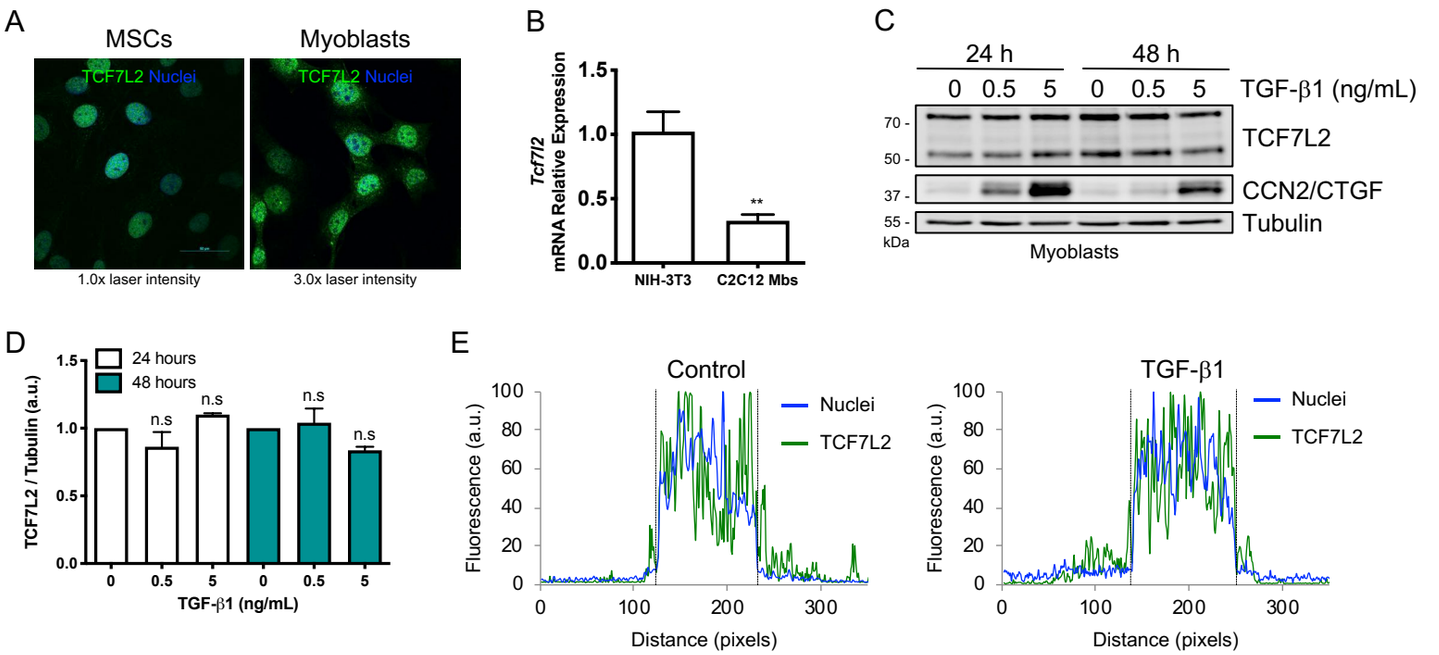

Fig. S8. The expression of TCF7L2 is not affected by TGF-β signaling in C2C12 myoblasts.

(A) Confocal images showing TCF7L2 localization in C3H/10T1/2 MSCs and C2C12 myoblasts cell types. Nuclei were stained with Hoechst (blue). Laser intensities (low vs high) were manually adjusted to show similar intensities of TCF7L2 fluorescence in both cell types. (B) *Tcf7l2* mRNA expression levels were analyzed by quantitative PCR in proliferating NIH-3T3 fibroblasts and C2C12 myoblasts. **P<0.005 by two-tailed Student's t-test. n=3. (C) Representative western blot analysis of three independent experiments, showing TCF7L2 and CCN2/CTGF protein levels in TGF-β1-treated C2C12 myoblasts at different concentrations for 24 or 48 h. Tubulin was used as the loading control. (D) Quantification of TCF7L2 protein levels. n.s, not significant by one-way ANOVA with Dunnett's post-test; n=3. (E) Label-distribution graph showing the fluorescence intensity of TCF7L2 and Hoechst along the cell axis. Distance is shown in pixels. Dotted lines show the nucleus-cytoplasm boundary. (a.u.: arbitrary units).

Table S1: Primers used in RT-qPCR

Gene	Forward primer (5'-3')	Reverse primer (5'-3')
Tcf7	GCCAGAAGCAAGGAGTTCAC	ACTGGGCCAGCTCACAGTAT
Lef1	CGCTAAAGGAGAGTGCAGCTA	GCTGTCTCTCTTTCCGTGCT
Tcf7l1 (Tcf3)	TGGTCAACGAATCGGAGAAT	TCACTTCGGCGAAATAGTCG
Tcf7l2 (Tcf4)	GAGATGAGAGCGAAGGTGGT	CGGCTGCTTGTCTCTTTTTC
Axin2	ACTGACCGACGATTCCATGT	CTGCGATGCATCTCTCTCTG
Sox9	CTCCGGCATGAGTGAGGT	TCGCTTCAGATCAACTTTGC
Ccnd1	CCCAACAACTTCCTCTCCTG	TCCAGAAGGGCTTCAATCTG
Ctnnb1	AAGGCTTTTCCCAGTCCTTC	CCCTCATCTAGCGTCTCAGG
Nfatc1	AACGCCCTGACCACCGATAGCACT	CCCGGCTGCCTTCCGTCTCATA
18S	TGACGGAAGGGCACCACCAG	CACCACCACCCACGGAATCG