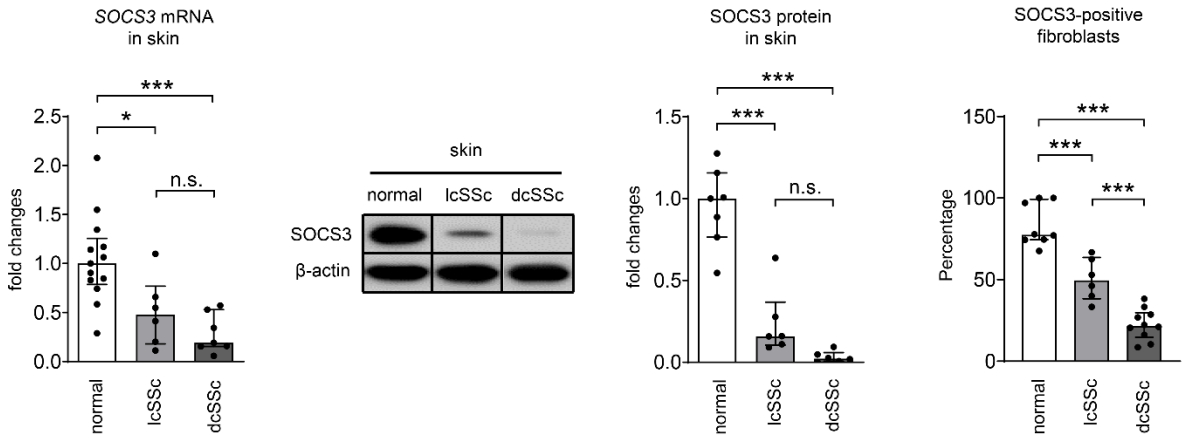
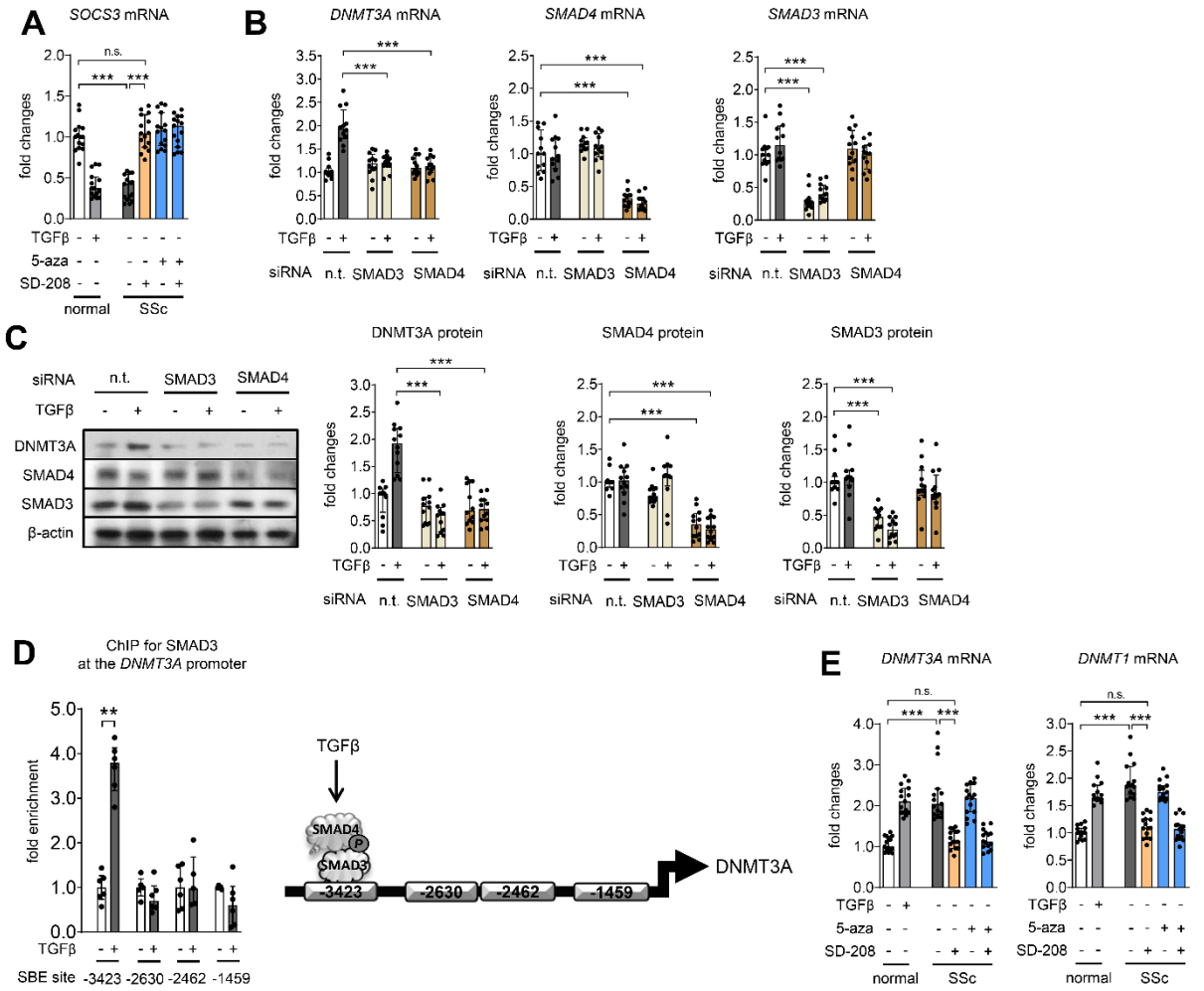
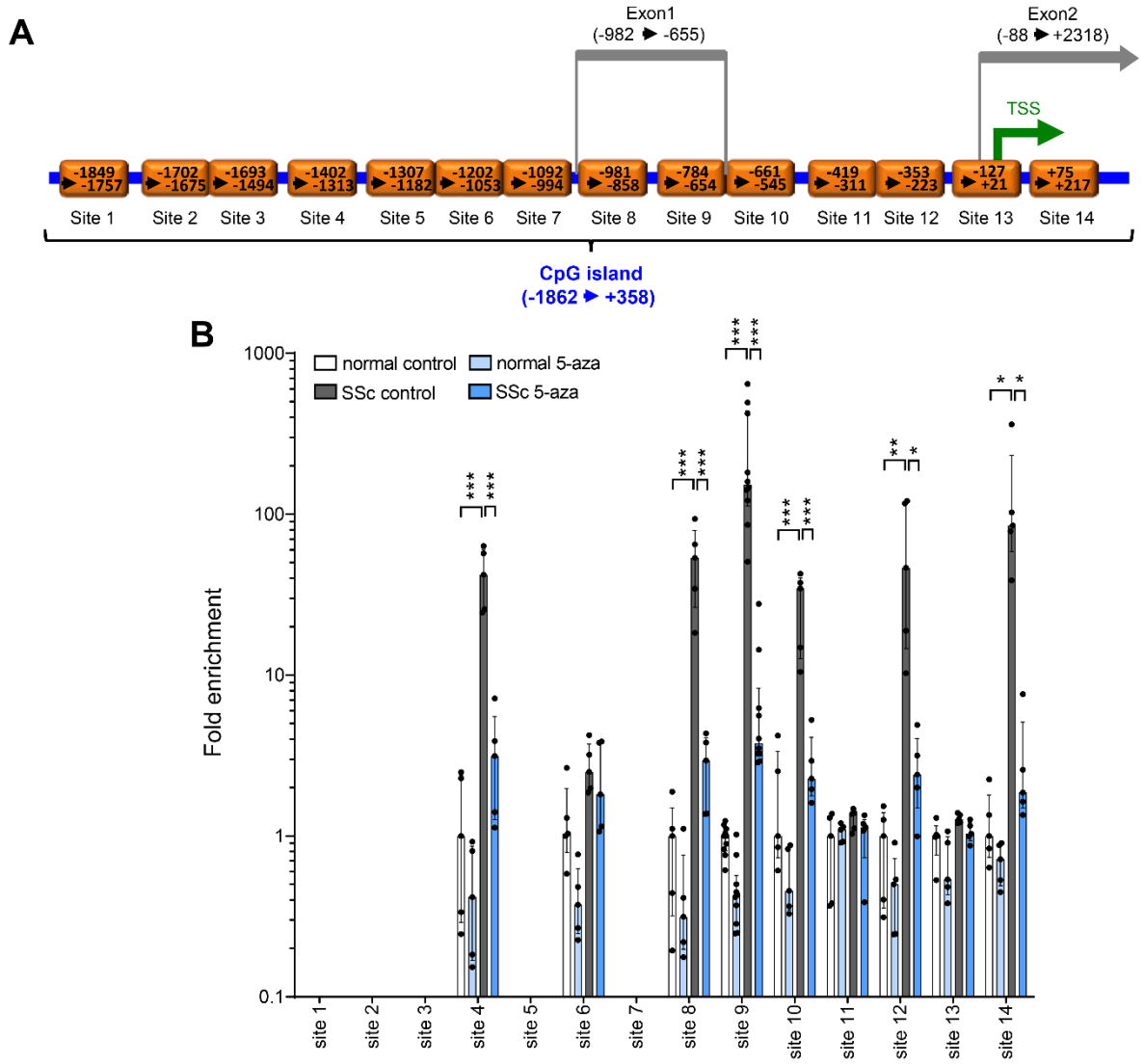


Supplementary Figure 1: Expression of SOCS3 in limited- and diffuse-cutaneous SSc. mRNA (n = 14 for normal skin samples, n = 7 for both lcSSc and dcSSc skin samples) and protein levels (n = 7 for normal skin samples, n = 6 for both lcSSc and dcSSc skin samples) and percentage of SOCS3-positive fibroblasts (n = 8 for normal skin samples, n = 6 for lcSSc and n = 10 for dcSSc skin samples) in normal skin and in the skin of patients with limited- (lcSSc) or diffuse-cutaneous SSc (dcSSc).
Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.



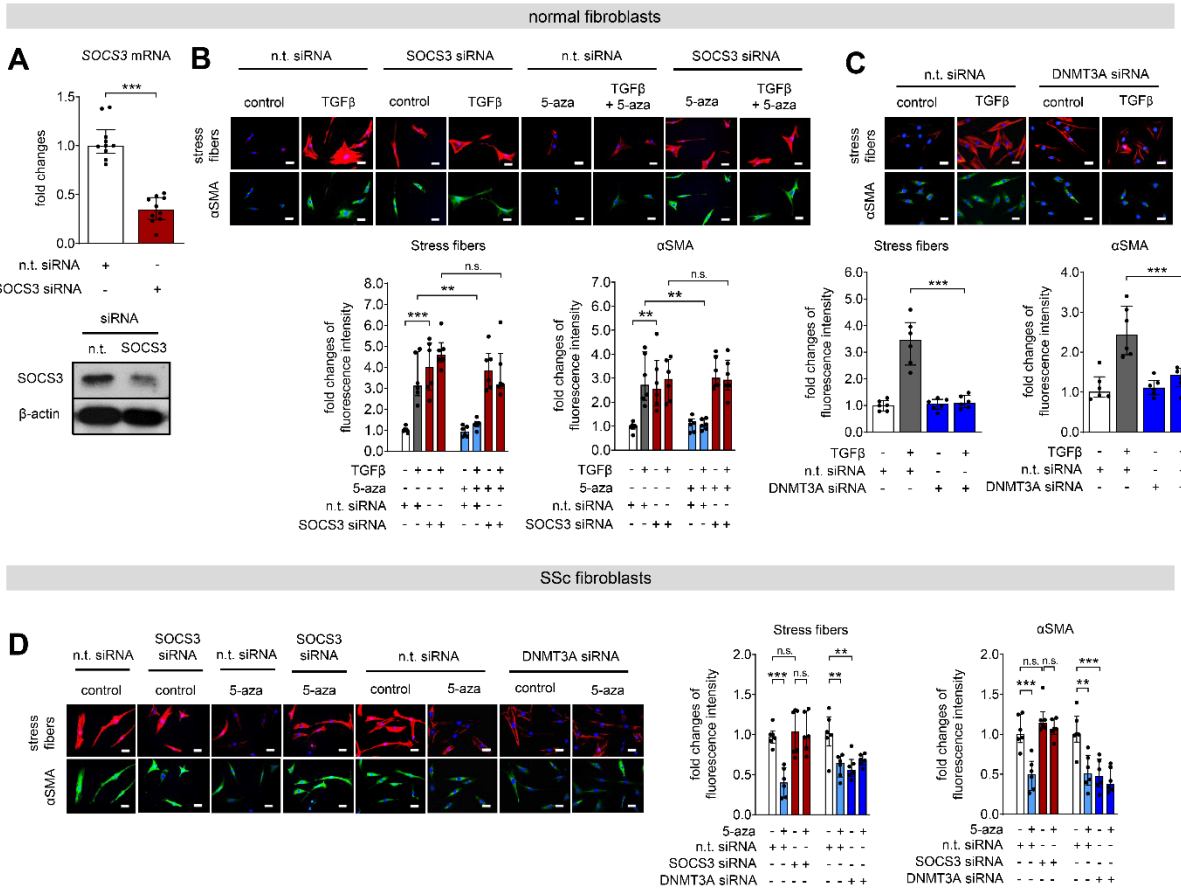
Supplementary Figure 2: TGFβ induces DNMT3A expression via canonical SMAD signaling. (A) *SOCS3* mRNA levels in SSc fibroblasts incubated with the TBRI kinase inhibitor SD-208 (n = 5 fibroblast lines from different donors with three technical replicates each). **(B)** Changes in the mRNA levels of *DNMT3A*, *SMAD3* and *SMAD4* in TGFβ-stimulated fibroblasts upon transfection with siRNA against *SMAD3* or *SMAD4* (n = 6 fibroblast lines from different donors with two technical replicates each). **(C)** Protein levels of DNMT3A, SMAD3 and SMAD4 in TGFβ-stimulated fibroblasts upon transfection with siRNA against *SMAD3* or *SMAD4* (n = 6 fibroblast lines from different donors with two technical replicates each). **(D)** Binding of SMAD3 on SMAD-binding (SBE) sites in the *DNMT3A* promoter as analyzed by ChIP assays (n = 3 fibroblast lines from different donors with two technical replicates each). **(E)** Changes in the mRNA levels of *DNMT3A* and *DNMT1* in SSc fibroblasts incubated with the TBRI kinase inhibitor SD-208 (n = 5 fibroblast lines from different donors with three technical replicates each).

Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.

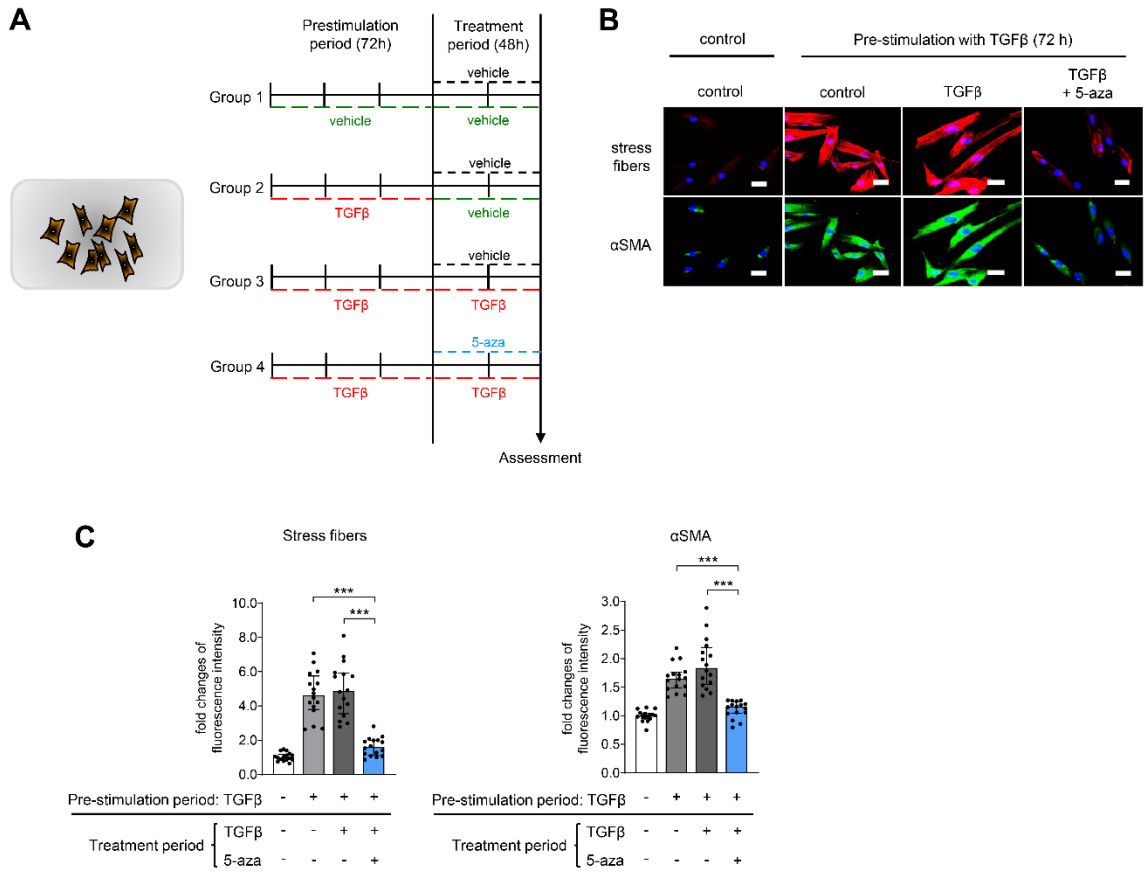


Supplementary Figure 3: The promoter of *SOCS3* is hypermethylated in SSc fibroblasts. **(A)** Scheme of the CpG island within the *SOCS3* promoter region and the sites analyzed by MeDIP. **(B)** Bar graph with single values of all sites analyzed by MeDIP-qPCR (n = 5 fibroblast lines from different donors).

Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.

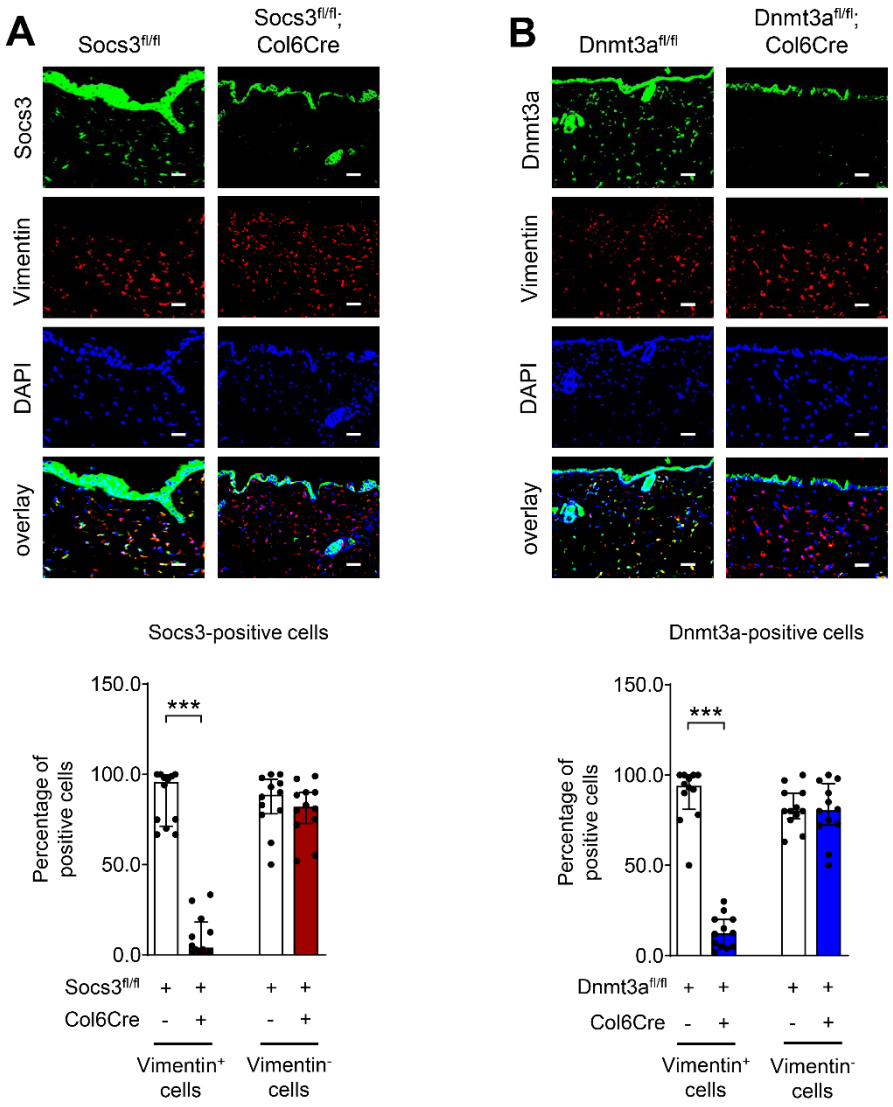


Supplementary Figure 4: Silencing of SOCS3 induces myofibroblast differentiation, while knockdown of DNMT3A prevents it. (A) mRNA and protein levels of SOCS3 upon transfection with SOCS3 siRNA in normal dermal fibroblasts (n = 5 fibroblast lines from different donors with two technical replicates each). **(B, C)** Representative stainings and quantitation of stress fibers (red) and of αSMA (green) upon knockdown of **(B)** SOCS3 or **(C)** DNMT3A in normal fibroblasts (n = 3 fibroblast lines from different donors with two technical replicates each; magnification: 200x, Scale bar: 250 µm). **(D)** Representative stainings and quantitation of stress fibers (red) and of αSMA (green) upon knockdown of SOCS3 or DNMT3A in SSc fibroblasts (n = 3 fibroblast lines from different donors with two technical replicates each; magnification: 200x, Scale bar: 250 µm).
Data are depicted as the median with interquartile range. Each dot represents an individual result. Mann-Whitney U test (panel A) or one-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.

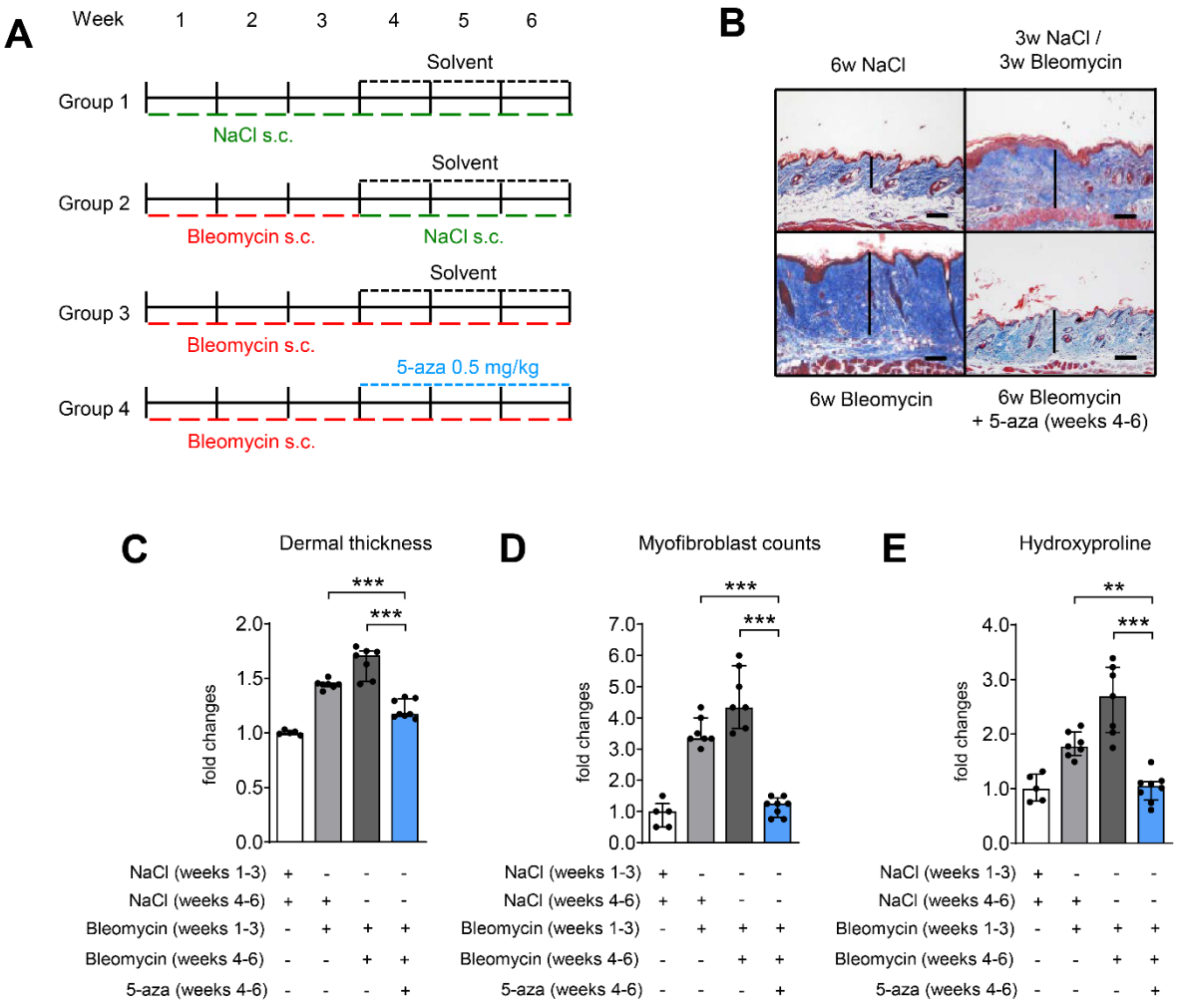


Supplementary Figure 5: Effects of 5-aza on the persistence of a pre-established, TGFβ-induced myofibroblast phenotype of cultured fibroblasts. (A) Graphical scheme of the experimental setup. **(B, C)** Representative stainings **(B)** and quantitation **(C)** of stress fibers (red) and of αSMA (green) upon treatment with 5-aza in chronically pre-stimulated normal fibroblasts (n = 8 fibroblast lines from different donors with two technical replicates each; magnification: 200x, Scale bar: 250 µm).

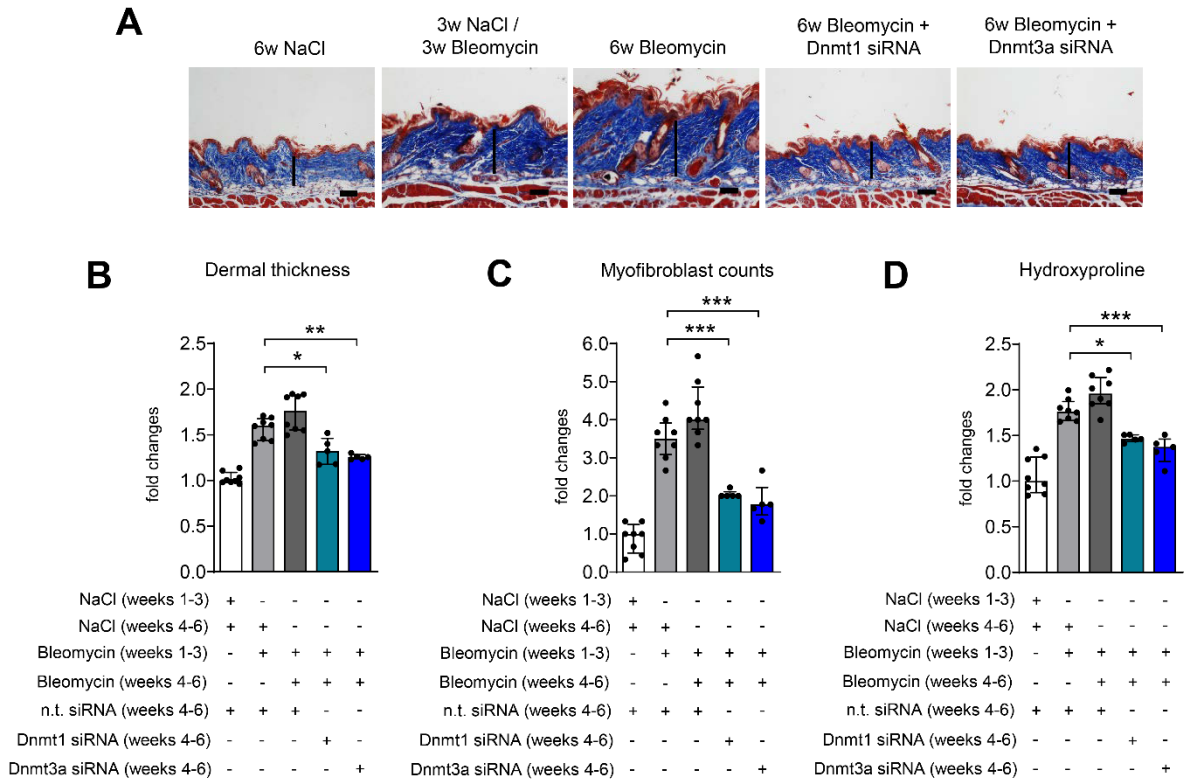
Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.



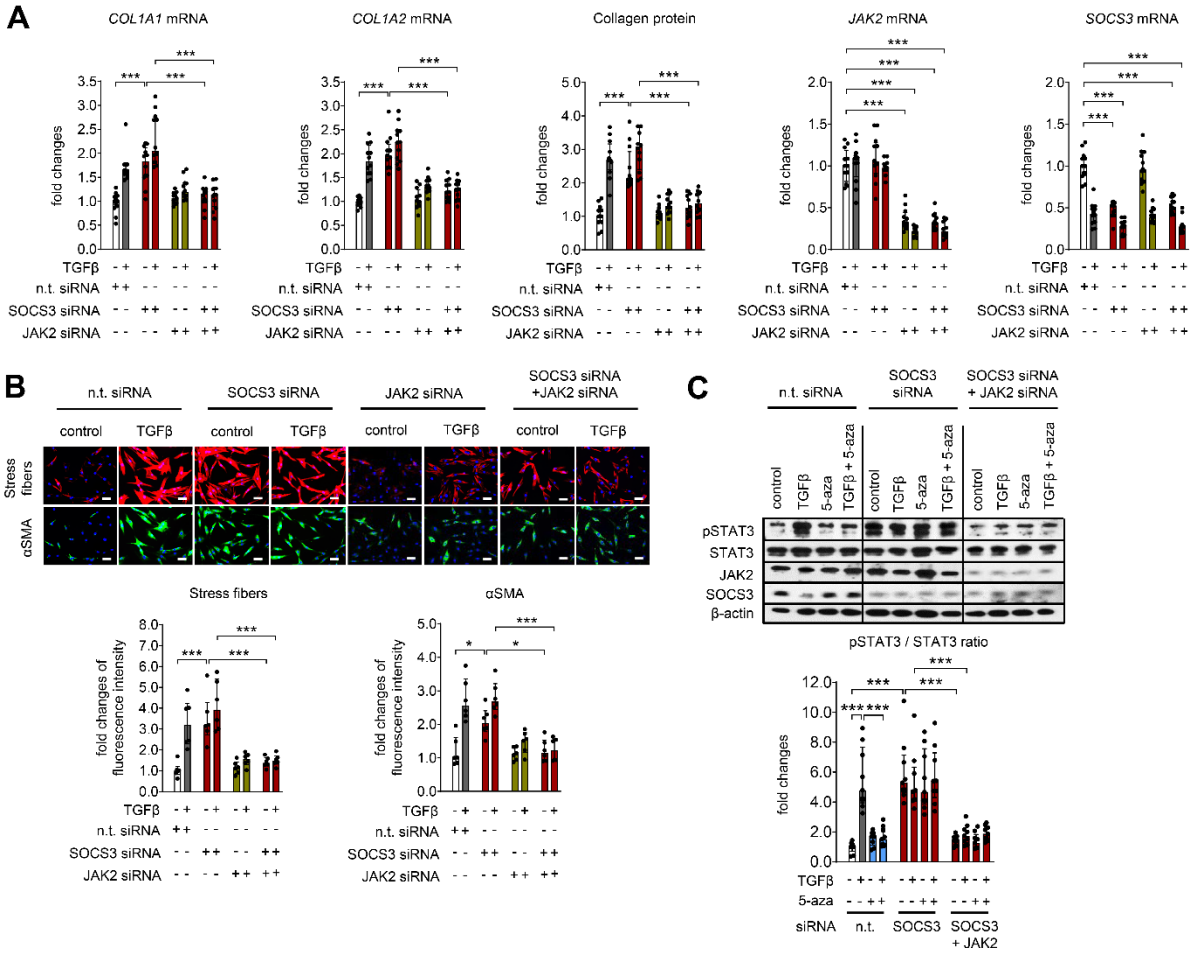
Supplementary Figure 6: Expression of Socs3 and Dnmt3a in the skin of mice with fibroblast-specific depletion of either Socs3 or Dnmt3a. (A) Representative images of immunofluorescence stainings for Socs3 and Vimentin in *Socs3$^{fl/fl}$* and *Socs3$^{fl/fl}$;Col6Cre* mice. **(B)** Co-staining for Dnmt3a and Vimentin in *Dnmt3a$^{fl/fl}$* and *Dnmt3a$^{fl/fl}$;Col6Cre* mice.
All stainings are shown at 200x magnification (n = 4 mice per group with three analyzed sections each; Scale bar: 200 µm).
Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.



Supplementary Figure 7: Effects of 5-aza on pre-established bleomycin-induced dermal fibrosis. (A) Graphical scheme of the experimental setup for the treatment of pre-established fibrosis. **(B)** Representative images of trichrome-stained sections at 100x magnification (Scale bar: 250 µm). **(C-E)** Relative changes of dermal thickness **(C)**, myofibroblast counts **(D),** and hydroxyproline content **(E)** ($n \geq 5$ mice per group).
Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.

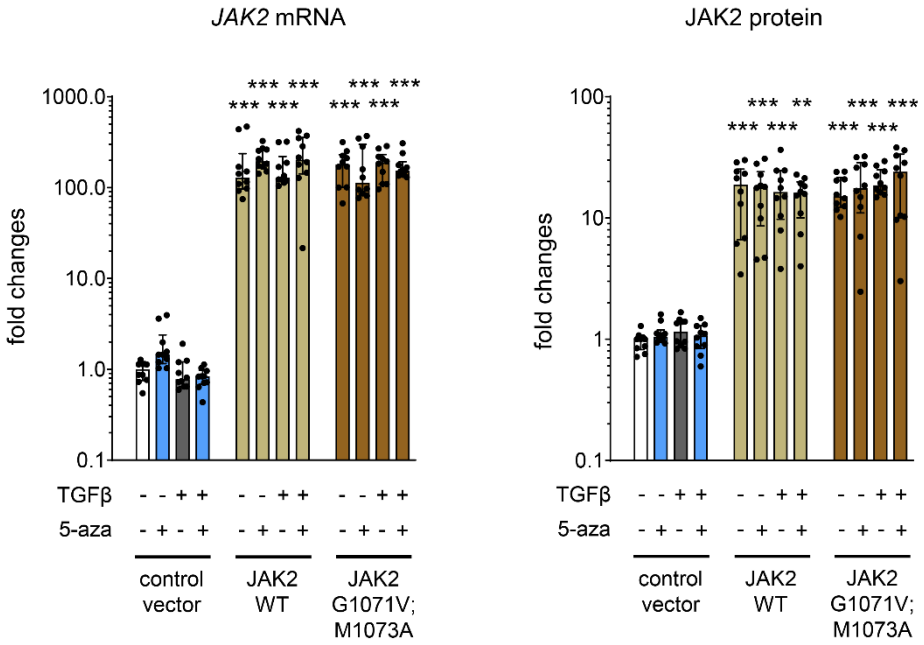


Supplementary Figure 8: Knockdown of Dnmt1 and Dnmt3a in pre-established bleomycin-induced dermal fibrosis. (A) Representative images of trichrome-stained sections at 100x magnification (Scale bar: 250 µm). **(B-D)** Relative changes of dermal thickness **(B)**, myofibroblast counts **(C),** and hydroxyproline content **(D)** (n = 8 mice per group for control groups with non-targeting siRNAs and n = 5 mice per group for treatment groups with target siRNAs against *Dnmt1* and *Dnmt3a*).
Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.

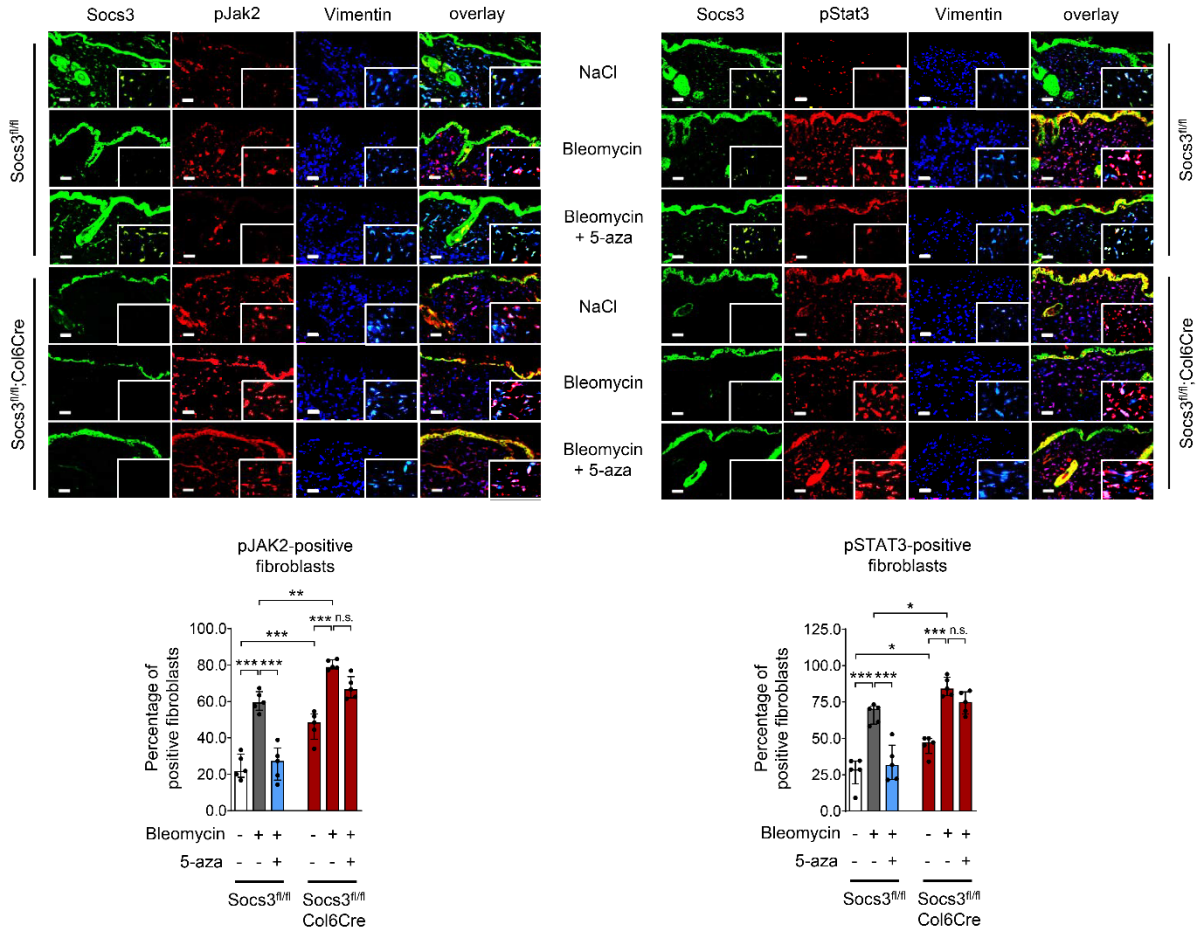


Supplementary Figure 9: SOCS3 regulates TGFβ-induced fibroblast activation by inhibition of JAK2-STAT3 signaling. (A) mRNA levels of *COL1A1*, *COL1A2*, *JAK2*, and *SOCS3*, and collagen protein content in cell culture media upon individual or combined siRNA-mediated knockdown of JAK2 and SOCS3 in normal dermal fibroblasts (n = 6 fibroblast lines from different donors with two technical replicates each). **(B)** Representative stainings and quantitation of stress fibers (red) and αSMA (green) upon individual or combined knockdown of SOCS3 and JAK2 in normal fibroblasts (n = 3 fibroblast lines from different donors with two technical replicates each; magnification: 200x; Scale bar: 250 µm). **(C)** Representative Western blot for p-STAT3, STAT3, JAK2 and SOCS3, and quantitation of the pSTAT3 / STAT3 ratio upon knockdown of JAK2 and SOCS3 (n = 3 fibroblast lines from different donors with three technical replicates each).

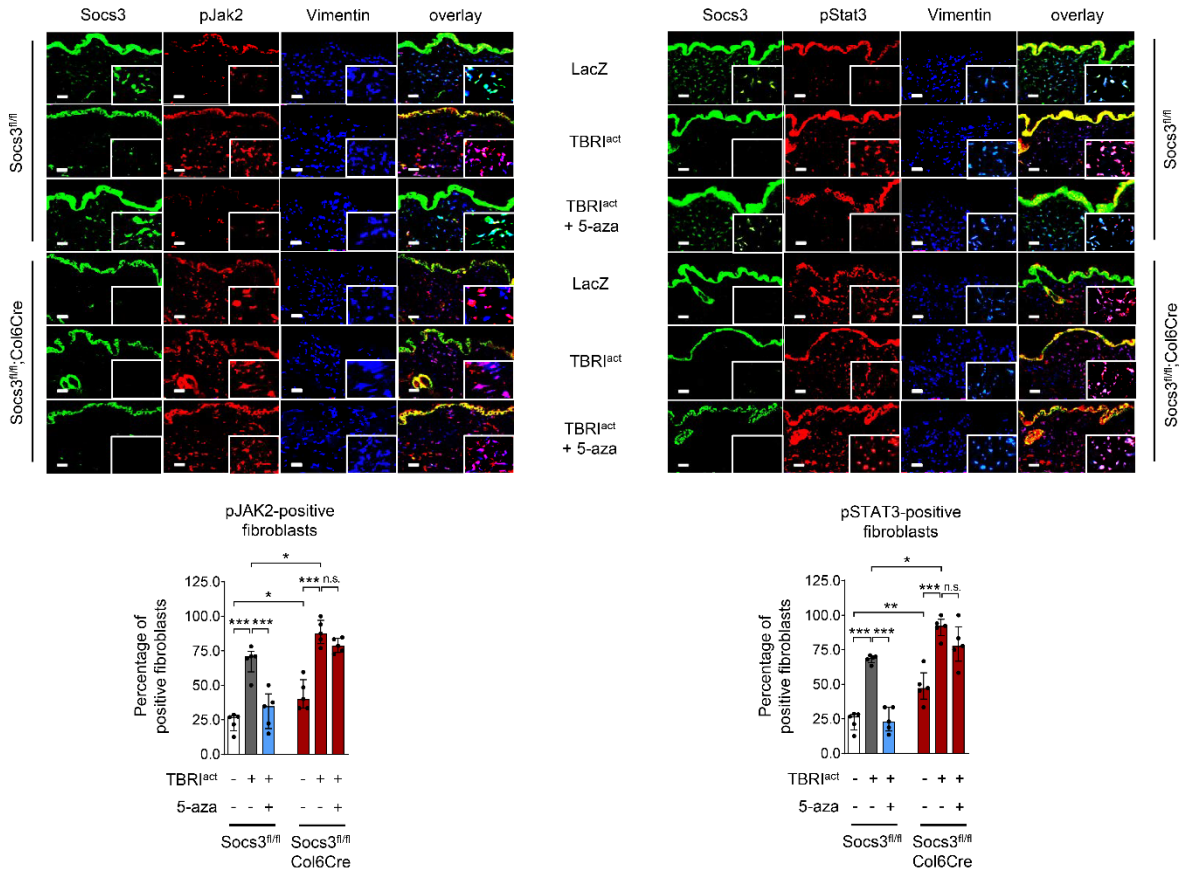
Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.



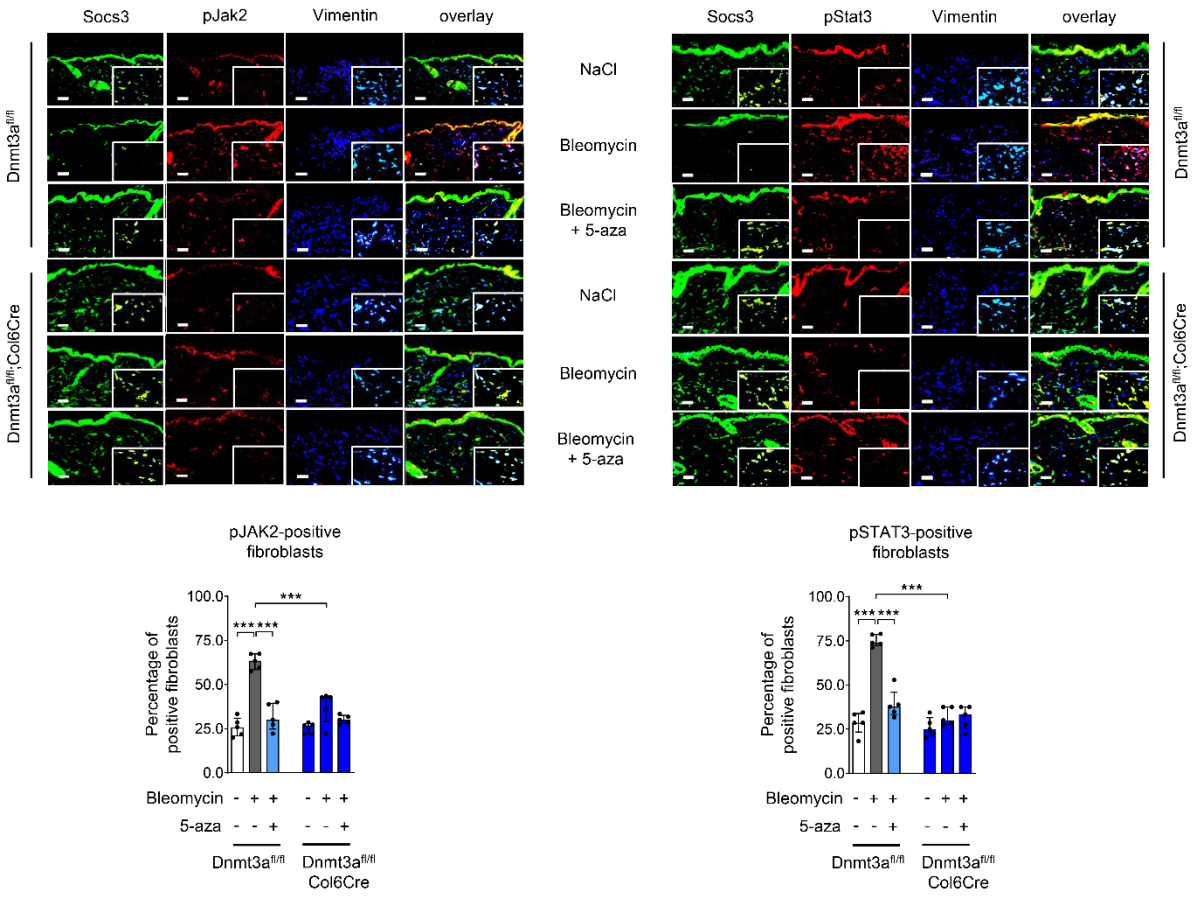
Supplementary Figure 10: mRNA and protein levels of JAK2 upon overexpression of wildtype JAK2 (JAK2-WT) or mutated JAK2 with a defective SOCS3 bindings site (JAK2-G1071V;M1073A) in dermal fibroblasts from healthy individuals (n = 5 fibroblast lines from different donors with two technical replicates each). Significance was tested against untreated cells transfected with control vector.
Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.



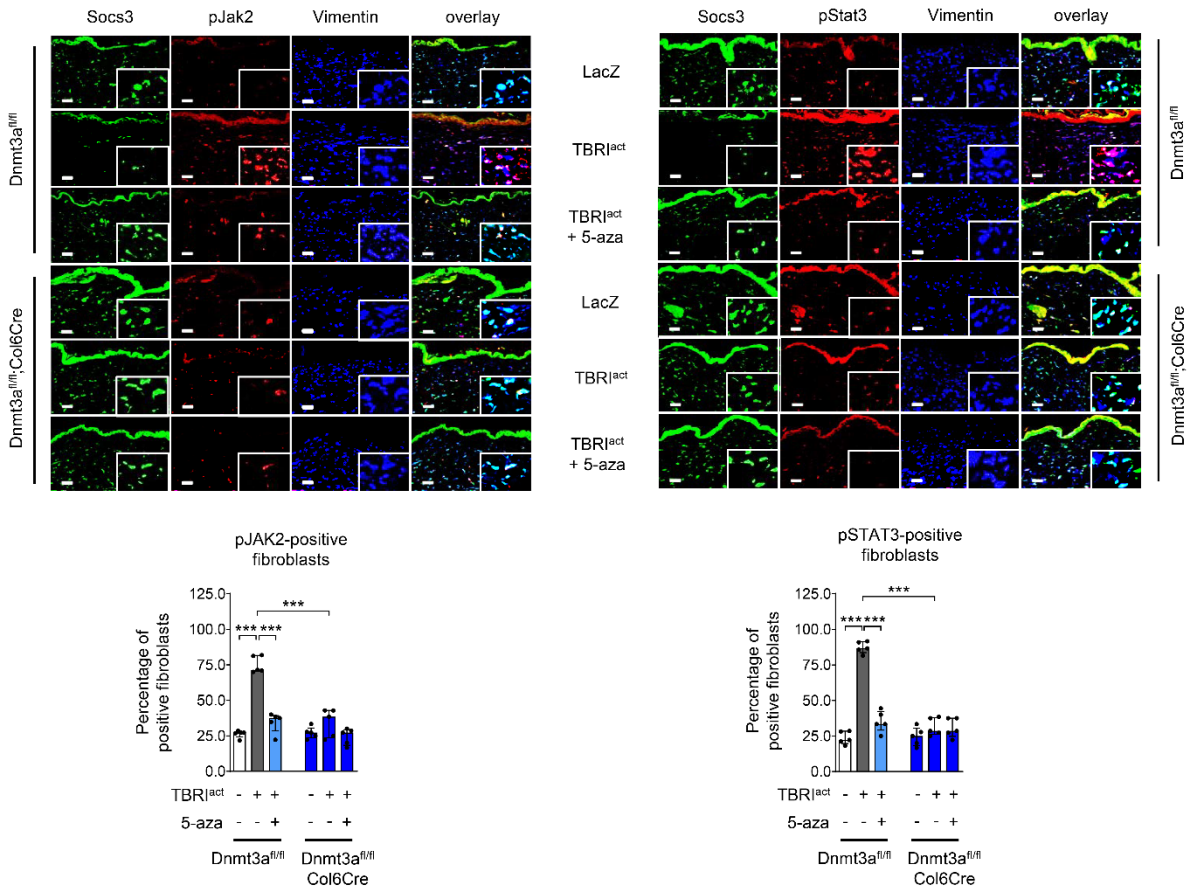
Supplementary Figure 11: Fibroblast-specific deletion of Socs3 promotes accumulation of phosphorylated Jak2 and Stat3 in bleomycin-induced fibrosis. Representative immunofluorescence stainings and quantitation for pJak2 (left) or pStat3 (right) costained with Socs3 and vimentin in fibroblasts in mice with conditional knockout of Socs3 challenged with bleomycin (n = 5 mice per group).



Supplementary Figure 12: Fibroblast-specific deletion of Socs3 promotes accumulation of phosphorylated Jak2 and Stat3 in TBRI^{act}-induced fibrosis. Representative stainings and quantitation for pJak2 (left) or pStat3 (right) with Socs3 and Vimentin in fibroblasts in mice with conditional knockout of Socs3 overexpressing TBRI^{act} (n = 5 mice per group).
Images are shown at 200x (Scale Bar: 100 µm) and 600x magnification.
Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.



Supplementary Figure 13: Fibroblast-specific deletion of Dnmt3a reduces accumulation of phosphorylated Jak2 and Stat3 in Bleomycin-induced fibrosis. Representative immunofluorescence stainings and quantitation for pJak2 (left) or pStat3 (right) costained with Socs3 and Vimentin in fibroblasts in mice with conditional knockout of Dnmt3a challenged with bleomycin (n = 5 mice per group).



Supplementary Figure 14: Fibroblast-specific deletion of Dnmt3a reduces accumulation of phosphorylated Jak2 and Stat3 in TBRI^{act}-induced fibrosis. Representative stainings and quantitation for pJak2 (left) or pStat3 (right) with Socs3 and Vimentin in fibroblasts in mice with conditional knockout of Dnmt3a overexpressing TBRI^{act} (n = 5 mice per group).
Images are shown at 200x (Scale Bar: 100 µm) and 600x magnification.
Data are depicted as the median with interquartile range. Each dot represents an individual result. One-way ANOVA with Tukey's range test as post hoc analysis was used for statistical analyses.

Supplementary Tables

	sense (5' -> 3')	**company**
human SOCS3	GAA-GAG-CCU-AUU-ACA-UCU-A	Eurogentec
human DNMT3A	CAG-GAG-AUG-AUG-UCC-AAC-CC	
human DNMT1	GAA-GAG-ACG-UAG-AGU-UAC-A	
human JAK2	GAA-CAG-GAU-UUA-CAG-UUA-U	
human SMAD3	ON-TARGETplus Human SMAD3 siRNA - SMARTpool (L-020067-00-0005)	Dharmacon
human SMAD4	ON-TARGETplus Human SMAD4 siRNA - SMARTpool (L-003902-00-0005)	
murine Dnmt3a	GAA-CAA-GCA-GAU-GAU-UGA-A	
murine Dnmt1	CAC-CUU-UCA-UGA-UGU-GAA-A	

Supplementary Table 1: siRNA sequences

		sequence (5' -> 3')
methylation-specific SOCS3	forward	GGAGATTTTAGGTTTTCGGAATATTTC
	reverse	CCCCCGAAACTACCTAAACGCCG
unmethylation-specific SOCS3	forward	GTTGGAGATTTTAGGTTTTTGGAATATTTT
	reverse	AAACCCCCAAAACTACCTAAACACCA

Supplementary Table 2: Sequences of primers used for methylation-specific PCR.

	sequence (5' -> 3')
human SOCS3 fwd	TCA AGA CCT TCA GCT CCA AGA
human SOCS3 rev	CAC TGC GTT CAC CAC CAG
murine Socs3 fwd	GCG CCA CTT CTT CAC GTT
murine Socs3 rev	GGT TCT TGG TCC CCG ACT
human DNMT1 fwd	GCC TGA GAA CAC CCA CAA GT
human DNMT1 rev	TGA TGT CTG CGT GGT AGC TC
human DNMT3A fwd	ATC CAT GGC CCA GGA CTC
human DNMT3A rev	AGT CCC CAT TGG GTA ATA GCT C
human DNMT3B fwd	TGTTTGTCTTGTGGCAGGAA
human DNMT3B rev	TCAAAGAGAGGGTGGAAGGA
human SMAD3 fwd	TGG GCT GAA GCG CAC TGA CC
human SMAD3 rev	CCG CGG CTC TTG CCC ACA T
human SMAD4 fwd	CAC GGC CCT GGT CGT CGT C
human SMAD4 rev	GCC ACC CAA ACC GCT CCG T
human COL1A1 fwd	ACG AAG ACA TCC CAC CAA TC
human COL1A1 rev	ATG GTA CCT GAG GCC GTT C
human COL1A2 fwd	GGT CAG CAC CAC CGA TGT C
human COL1A2 rev	CAC GCC TGC CCT TCC TT
MeDIP SOCS3 site 1 fwd	ACGCGGGCCGTAGGTT
MeDIP SOCS3 site 1 rev	AAACCTGGTTGGTCCGGTG
MeDIP SOCS3 site 2 fwd	CGCGTCAGGGTTGGCA
MeDIP SOCS3 site 2 rev	TTGGAGACGTGCGACAGTC
MeDIP SOCS3 site 3 fwd	GACTGTCGCACGTCTCCAA
MeDIP SOCS3 site 3 rev	CCCAACTGCGGGTCAGG
MeDIP SOCS3 site 4 fwd	CTCCAGGTCGGCCTCCTA
MeDIP SOCS3 site 4 rev	AGGCTGATTTCTGGCAGAGG
MeDIP SOCS3 site 5 fwd	GGAAAGTGTGAATGAGAAGTTGGG
MeDIP SOCS3 site 5 rev	GAGACAAAGCGCGACGAGA
MeDIP SOCS3 site 6 fwd	CCTCTCGTCGCGCTTTGT
MeDIP SOCS3 site 6 rev	GGCCGGCCTTCTTGTAATGT
MeDIP SOCS3 site 7 fwd	CTGCTGCGAGTAGTGACTAAAC
MeDIP SOCS3 site 7 rev	CGCGCTCGCGGGTATAT
MeDIP SOCS3 site 8 fwd	GCTCCGACTTGGACTCCCT
MeDIP SOCS3 site 8 rev	GAGGGGACCAGGAGAGGGA
MeDIP SOCS3 site 9 fwd	TCCTTTGTGGACTTCACGGC
MeDIP SOCS3 site 9 rev	CCTGGTCCCGAATCGAAGTC
MeDIP SOCS3 site 10 fwd	GGACCAGGTAGGAAGGAGGA
MeDIP SOCS3 site 10 rev	CCTACCTCGTCACCTCCCT
MeDIP SOCS3 site 11 fwd	CTACTGGACTGAGCGGCG
MeDIP SOCS3 site 11 rev	GGCGCAGCGTGGGAA
MeDIP SOCS3 site 12 fwd	CCTGGAGACCTAACTTCCGC
MeDIP SOCS3 site 12 rev	GATCCAGGCGCCTCACG

MeDIP SOCS3 site 13 fwd	TTCCGGGCACTCAACGC
MeDIP SOCS3 site 13 rev	AAACTTGCTGTGGGTGACCA
MeDIP SOCS3 site 14 fwd	CAGCTCCAAGAGCGAGTACC
MeDIP SOCS3 site 14 rev	TGTCGCGGATCAGAAAGGTG
ChIP DNMT3Aprom (SBE1: -3423) fwd	GGACCCTCATATGAGTGGAATCC
ChIP DNMT3Aprom (SBE1: -3423) rev	AGGGAGTCCTGACACCTGTT
ChIP DNMT3Aprom (SBE2: -2630) fwd	CCTGTCCTGATACTGCCACA
ChIP DNMT3Aprom (SBE2: -2630) rev	GGTTTAGCCTCTCGGCTTCT
ChIP DNMT3Aprom (SBE3: -2462) fwd	TCTGGAACCAACCCTGTAGC
ChIP DNMT3Aprom (SBE3: -2462) rev	GGTCAAGAGGTCCAAGGTGA
ChIP DNMT3Aprom (SBE4: -1459) fwd	CTTCATCTGTAGCGTGAGGAGA
ChIP DNMT3Aprom (SBE4: -1459) rev	ATATAACACGGCCCCAAACA

Supplementary Table 3: Sequences of primers used for qPCR.