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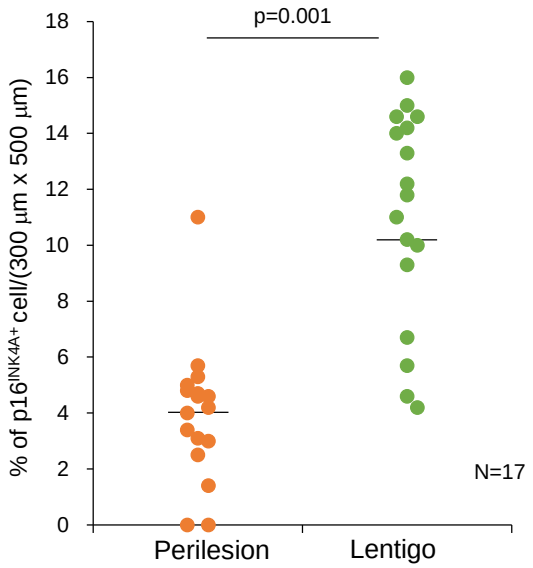

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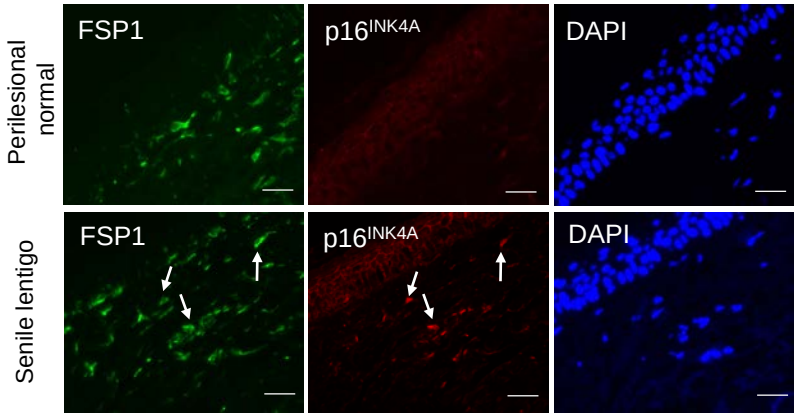

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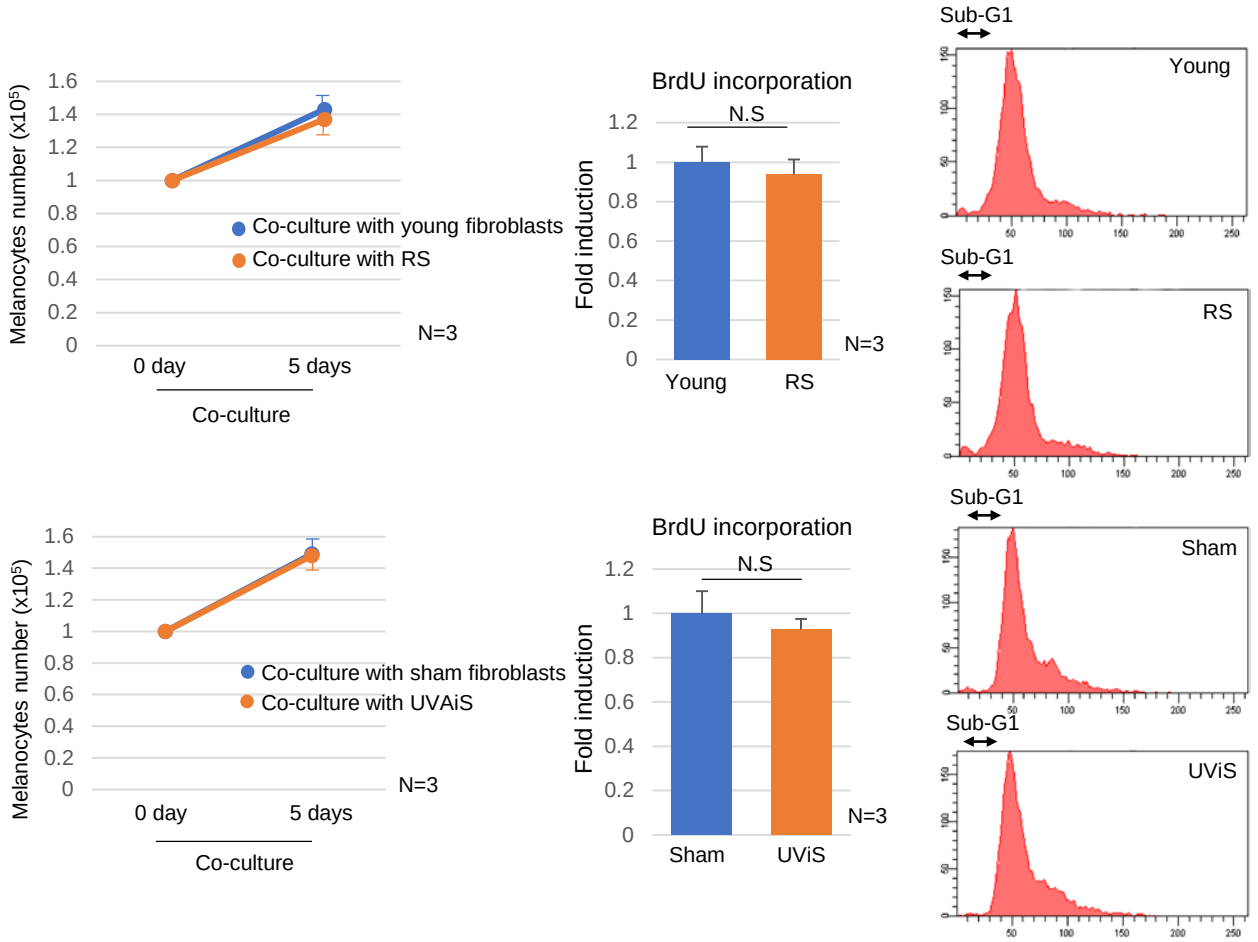

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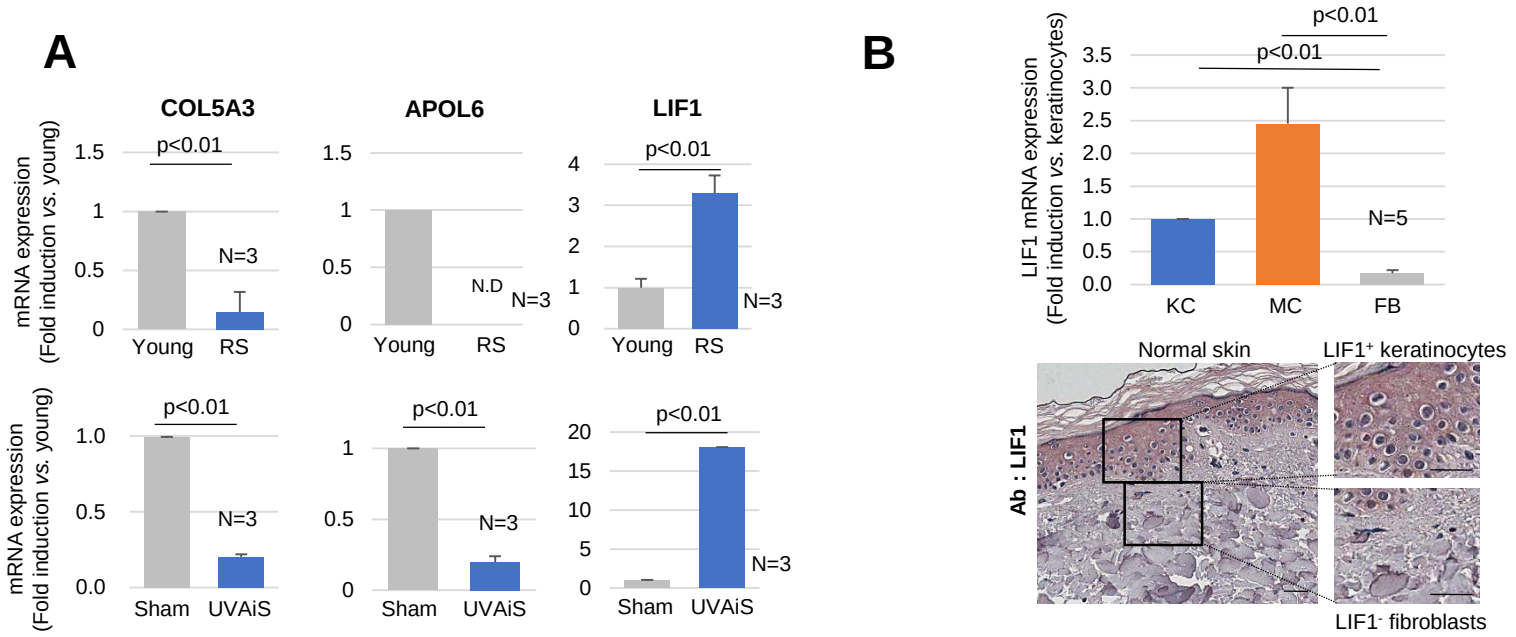

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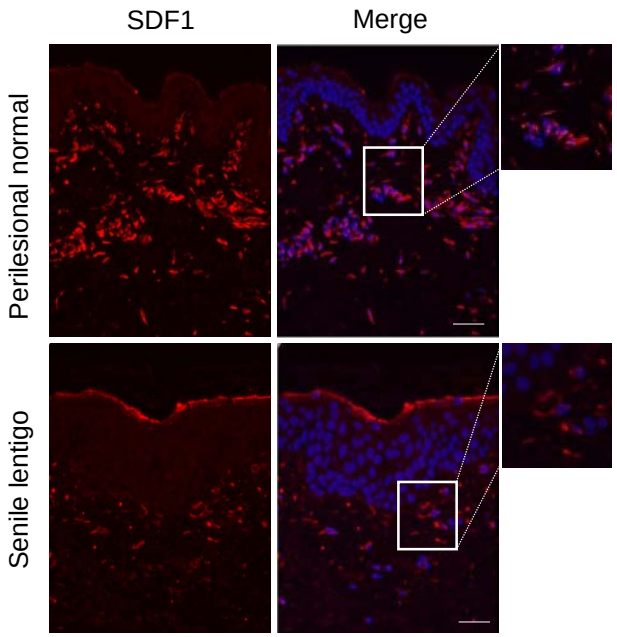

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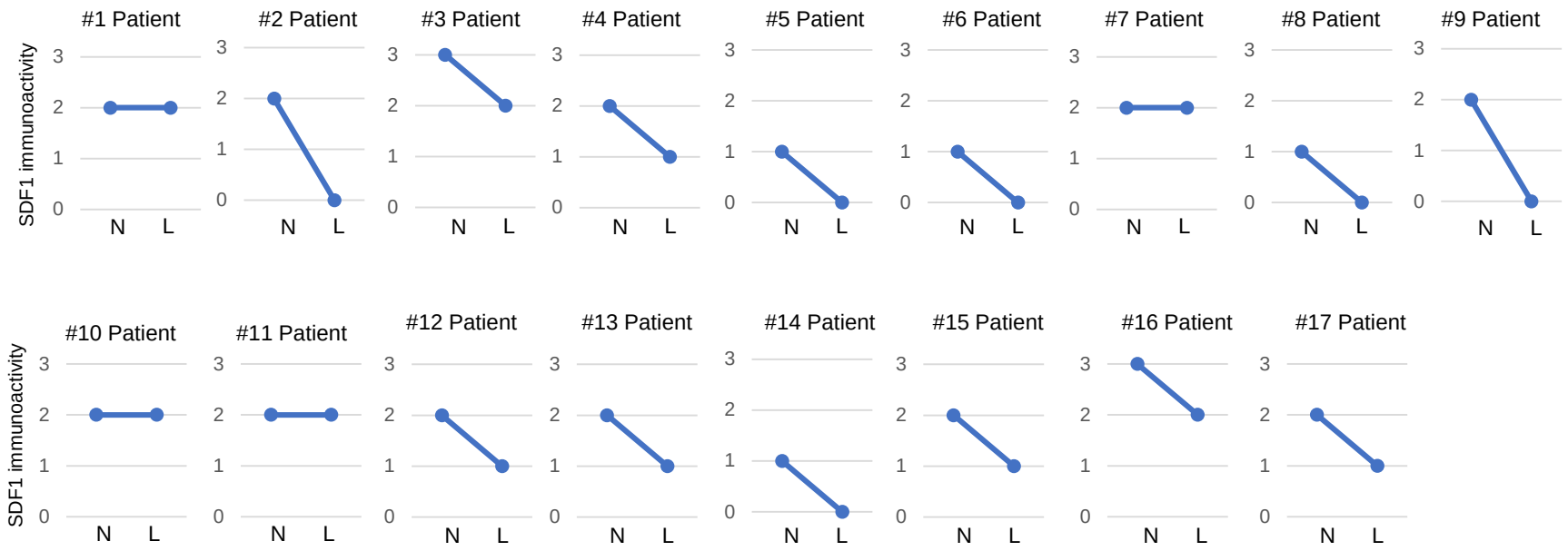

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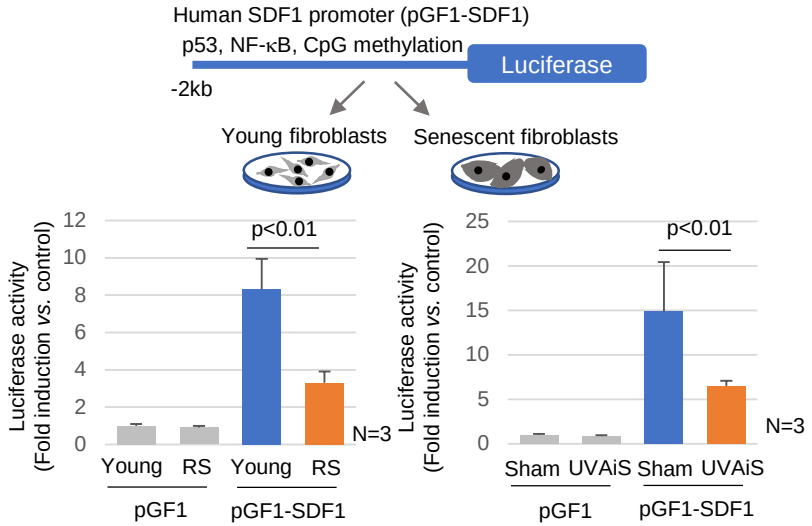

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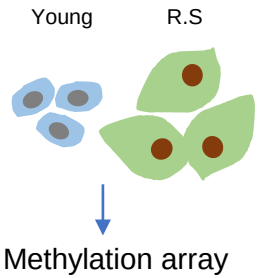
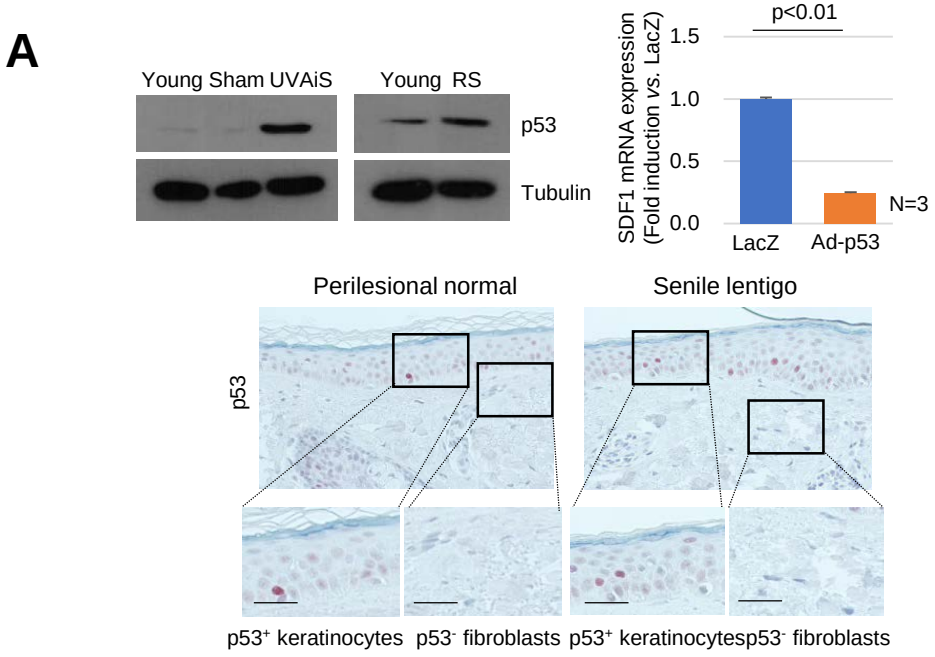
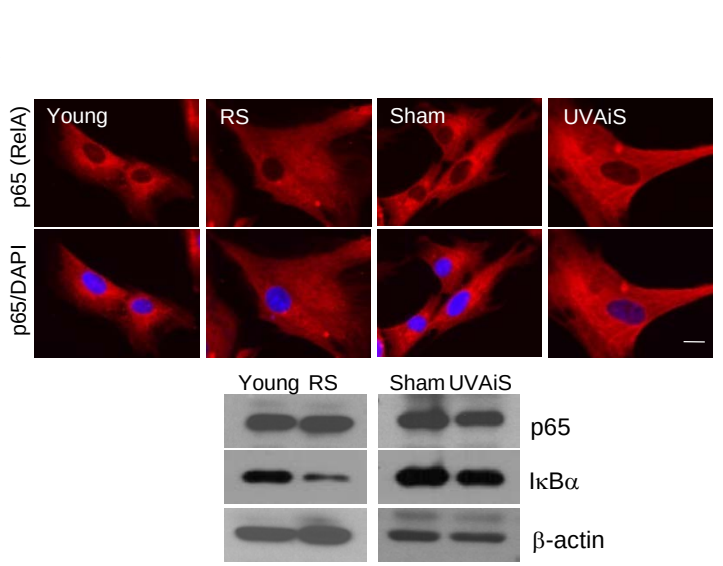


SDF1 CpG island methylation

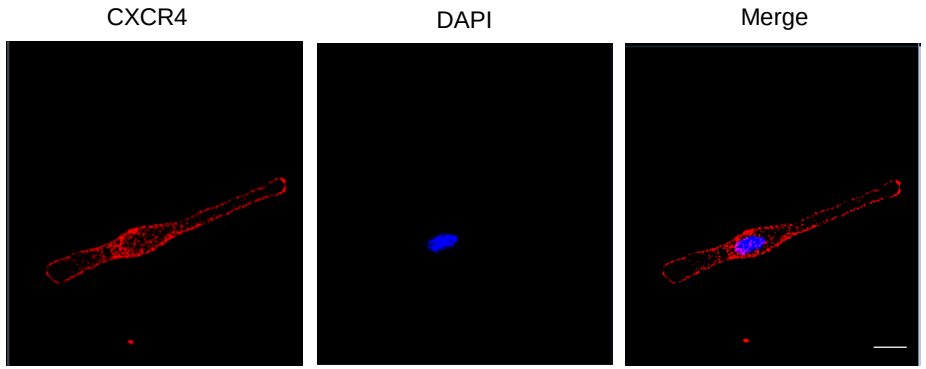
Target ID	R.S AVG Beta	Young AVG Beta	UCSC REFGENE GROUP
cg07001963	0.4433818	0.1477356	Body
cg2671843	0.2630038	0.04585296	TSS200
cg11267527	0.894617	0.6182697	TSS1500
cg18618334	0.7266957	0.3488797	TSS1500
cg19959917	0.8025302	0.5268313	Body

Supplement Figure S9





Supplement Figure S10



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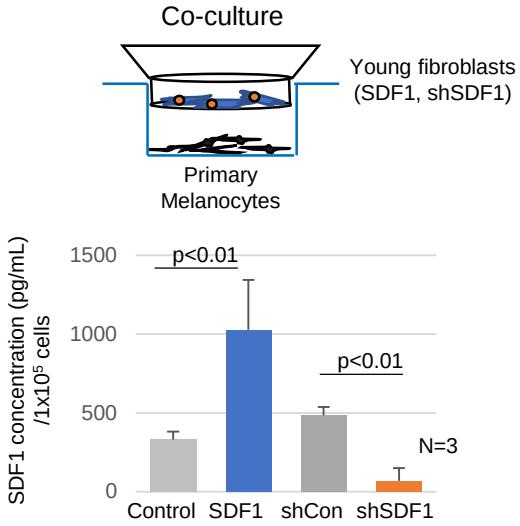

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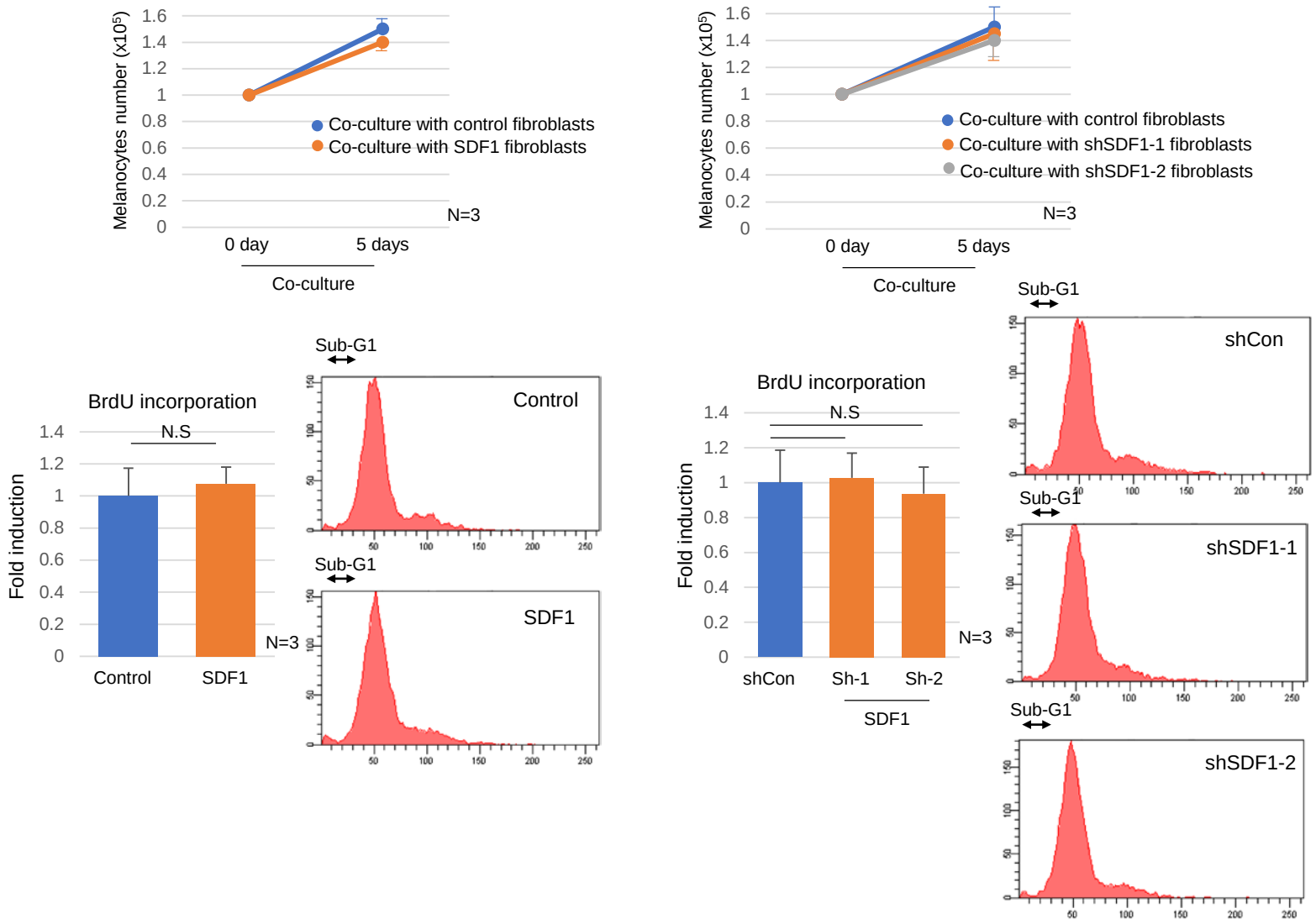

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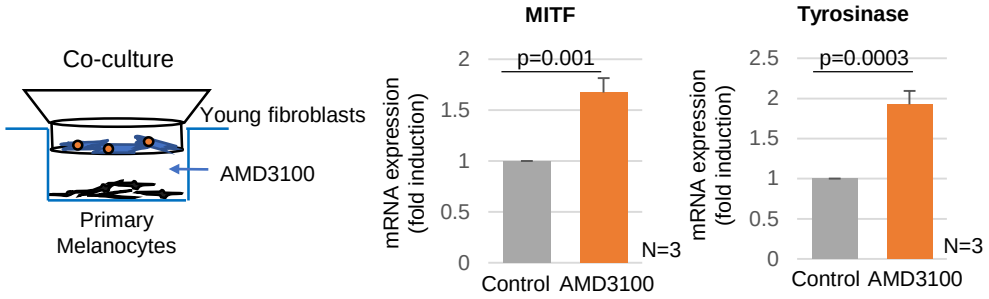

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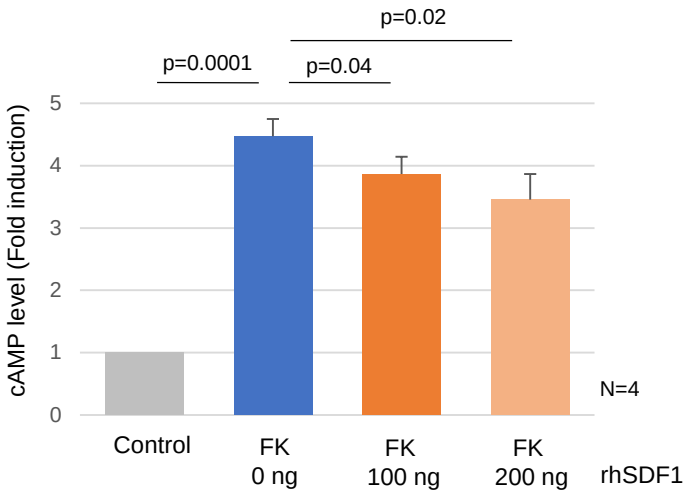

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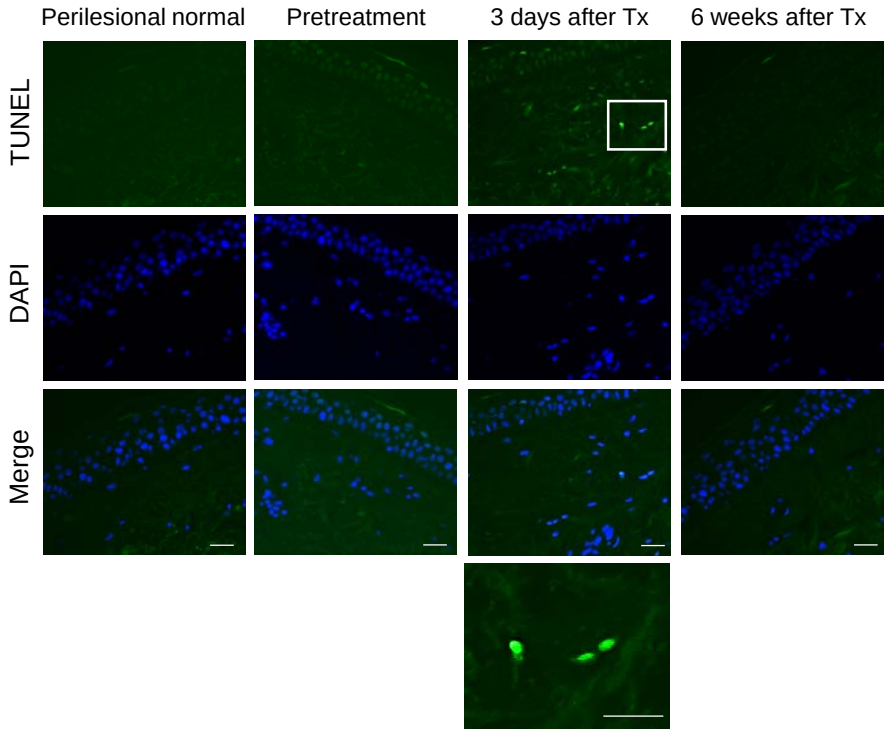

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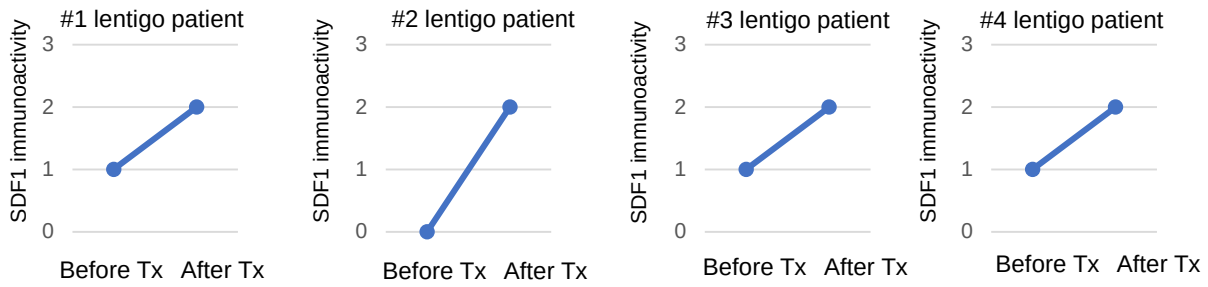

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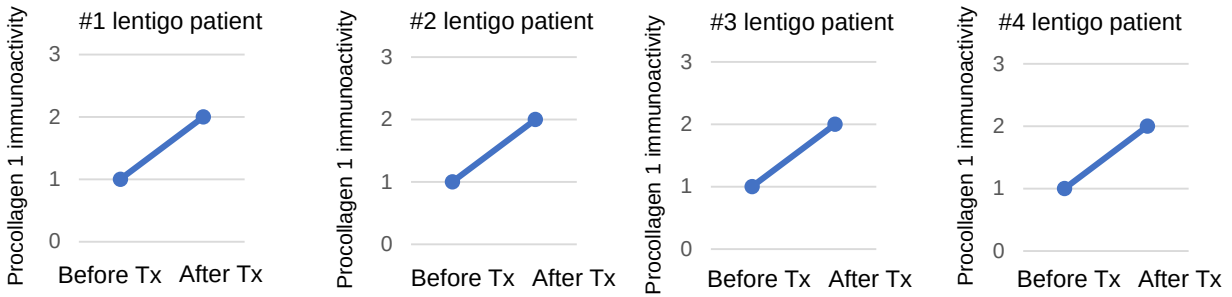

Supplement figure legends

Figure S1. Senescent cells in senile lentigo (SL). Fourteen cases of SL were stained with $p16^{INK4A}$ and positive spindle-shaped cells were counted and presented as a dotted graph (% of $p16^{INK4A}$-positive spindle-shaped cells/total spindle-shaped cells. *p* value, Wilcoxon test). Numbers indicate the means of percentages in each case.

Figure S2. Senescent fibroblasts in senile lentigo and perilesional normal. Immunostaining of fibroblast-specific protein 1 (FSP1, green) and $p16^{INK4A}$ (red). The scale bar indicates 50 μm

Figure S3. Effect of senescent fibroblasts in melanocyte proliferation. Melanocytes ($1x10^5$) were co-cultured with senescent fibroblasts or controls for five days. The numbers of melanocytes were analyzed (left panel). BrdU incorporation assay. Melanocytes were co-cultured with senescent or young fibroblasts for three days and BrdU incorporation was analyzed by ELISA (middle panel). FACS analysis. Melanocytes were co-cultured with senescent or young fibroblasts for three days. The sub-G1 population was analyzed by FACS (right panel). (*p* value, *t*-test)

Figure S4. (A) Real-time PCR analysis of target genes. N.D.: not detected. (B) LIF1 expression levels in skin cells. The upper panel shows the results of a real-time PCR analysis of LIF1 mRNA expression levels in cultured melanocytes (MC), keratinocytes (KC) and fibroblasts (FB). LIF1 immunostaining of normal human skin (lower panel, scale bar, 50 μm). (*p* value, *t*-test)

Figure S5. Immunohistochemical analysis of SDF1 expression level in perilesional and lentigo lesion skin. The scale bar indicates 50 μm.

Figure S6. Immunohistochemical analysis of SDF1 expression in perilesional and lentigo lesion skin. Seventeen cases of lentigo were stained with an anti-SDF1 antibody. The intensity levels were analyzed and are presented here as none (0), weak (1+), moderate (2+), and strong (3+). N and L indicate

perilesional normal skin and senile lentigo, respectively.

Figure S7. SDF1 transcriptional regulation. Two kilobases of human SDF1 promoter were cloned and inserted into a pGF1 vectors (pGF1-SDF1), generated a lentivirus. A control (empty pGF1) or SDF1-pGF1 lentivirus was infected into young, replicative senescent, sham or UVA-induced senescent fibroblasts, after which the luciferase activity was measured in each case with a luminometer. (*p* value, *t*-test)

Figure S8. DNA methylation profiles of replicative senescent fibroblasts. A methylation array was performed in young and replicative senescent fibroblasts. SDF1 CpG islands methylation is presented.

Figure S9. (A) SDF1 expression regulation by p53. The p53 expression levels were analyzed by western blotting in young, replicative and UVA-induced senescent fibroblasts (upper panel). Young fibroblasts were infected with Ad-LacZ (control) or a p53-expressing adenovirus (Ad-p53) for two days. The SDF1 mRNA expression levels were analyzed by real-time PCR. The lower panel shows the p53 immunostaining of SL skin samples (scale bar, 50 μm). (B) NF-κB signaling in senescent fibroblasts. Immunocytochemical staining of p65 (RelA) localization (upper panel, scale bar, 10 μm) and results of a western blotting analysis of IκBa degradation (lower panel). (*p* value, *t*-test)

Figure S10. Immunocytochemical analysis of CXCR4 in cultured melanocytes (Scale bar, 10 μm).

Figure S11. Fibroblasts were infected with a sh-Control (shCon), SDF1 or with the shSDF1 lentivirus and co-cultured with human primary melanocytes. SDF1 protein was measured by ELISA (lower panel). (*p* value, *t*-test)

Figure S12. Cell proliferation assay. Melanocytes ($1x10^5$) were co-cultured with fibroblasts infected with the SDF1 or shSDF1 lentivirus for five days and the numbers of melanocytes were analyzed. BrdU

incorporation assay. Melanocytes were co-cultured with control, SDF1 overexpressed or shSDF1 infected fibroblasts for three days. The degree of BrdU incorporation was then analyzed by ELISA. FACS analysis. Melanocytes were co-cultured with control, SDF1 overexpressed or shSDF1 infected fibroblasts for three days and Sub-G1 populations were analyzed by FACS. (*p* value, *t*-test)

Figure S13. AMD3100 increased pigmentation-related genes expression. Human primary melanocytes were treated with CXCR4 antagonist AMD3100 (1 μM) and co-cultured with human primary fibroblasts for three days. The MITF and tyrosinase mRNA expression levels were analyzed by real-time PCR. (*p* value, *t*-test)

Figure S14. SDF1 decreased forskolin-induced cAMP levels in melanocytes. Melanocytes were treated with rhSDF1 (0 to 200 ng/mL) for 10 min before a forskolin treatment (700 ng/mL) for 30 min. The cAMP levels were then analyzed. (*p* value, *t*-test)

Figure S15. Matched biopsies from four individual subjects, one pair (SL and perilesional normal) from untreated faces and a second pair from faces treated with RF, were assayed the apoptotic cells using TUNEL assay (scale bar, 50 μm).

Figure S16. Lentigo patients were treated with six instances of radiofrequency (RF). The SDF1 expression levels were analyzed using immunohistochemistry. The intensity levels are presented here as none (0), weak (1+), moderate (2+), and strong (3+) (n=4).

Figure S17. Lentigo patients were treated with six instances of radiofrequency (RF). The procollagen type 1 expression levels were analyzed using immunohistochemistry. The intensity levels are presented here as none (0), weak (1+), moderate (2+), and strong (3+) (n=4).