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**Background:** The aldehyde dehydrogenase (ALDH) superfamily comprises a group of 20 enzymes that catalyze aldehyde oxidation. Within this enzyme family, ALDH3A2 stands out for its central role in the oxidation of long-chain aldehydes. Of particular interest, the substrates of ALDH3A2 include also proflibrotic lipid mediators such as sphingosine 1-phosphate or leukotrienes, which have been reported to be deregulated in the context of SSc.

**Objectives:** We aimed to investigate the role of ALDH3A2 in fibrotic tissue remodeling in SSc.

**Methods:** Fibroblast-to-myofibroblast transition was analyzed by quantification of ACTA2/α-SMA, by assessment of stress fiber formation and mRNA and protein levels of type I collagens. ALDH3A2/α-SMA siRNAs were employed to specifically knockdown ALDH3A2 in dermal fibroblasts both in vitro and in vivo. Overexpression of ALDH3A2 was achieved by ALDH3A2-pcDNA transfection. The role of ALDH3A2 was investigated in three different mouse models: Bleomycin- and TGFβ-over, in vivo knockdown of ALDH3A2 in the skin of mice ameliorated dermal fibrosis and fibroblast-to-myofibroblast transition, reduced dermal thickening and impaired collagen deposition in the different murine skin models of fibrosis: Bleomycin-induced skin fibrosis and scleroderma transgenic mice, with fibroblast-specific inhibition of TGFβ receptor I (TBRICΔ). Target genes of ALDH3A2 in fibroblasts were identified by RNA sequencing.

**Results:** The expression of ALDH3A2 was modestly reduced in dermal fibroblasts of SSc skin as compared to matched healthy controls. This reduction in ALDH3A2 expression was phenocopied by activation of TGFβ signaling, whereas selective inhibition of TGFβ signaling prevented the downregulation of ALDH3A2 in experimental fibrosis. ALDH3A2 overexpression promoted fibroblast-to-myofibroblast transition with increased levels of α-SMA, enhanced formation of stress fibers and reduced collagen release. In contrast, knockdown of ALDH3A2 in dermal fibroblasts inhibited fibroblast activation and collagen release. Moreover, in vivo knockdown of ALDH3A2 in the skin of mice ameliorated dermal thickening, myofibroblast differentiation and collagen deposition in three different murine skin models of fibrosis: Bleomycin-induced skin fibrosis and sclerodermatous GvHD-as models of inflammatory stages of SSc and TBRICΔ-induced fibrosis as an inflammation-independent model of SSc. RNA sequencing of ALDH3A2-knockdown fibroblasts demonstrated that ALDH3A2 regulates the activity of a network of profibrotic developmental pathways including TGFβ, Wnt, Notch, and Hedgehog signaling.

**Conclusion:** We demonstrate that ALDH3A2 regulates a network of profibrotic pathways to control fibroblast activation and tissue fibrosis. ALDH3A2 is modestly downregulated in SSc fibroblasts as result of an endogenous, TGFβ-driven feedback loop. Although this modest downregulation is not sufficient to counterbalance the aberrant fibroblast activation in SSc, augmentation of this endogenous regulation by knockdown of ALDH3A2 demonstrates potent antifibrotic potential in experimental dermal fibrosis, thereby providing first evidence for ALDH3A2 as a target for antifibrotic therapies.

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