Treprostinil inhibits functional activation of scleroderma (SSc) vascular smooth muscle cells (vSMCs) by inhibiting Yap and activating PPARG signaling.

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Background: Progressive vascular wall thickness and fibrosis are the hallmarks of SSc vasculopathy. Overexpression of TGFB1 in SSc and activation of vSMCs are important steps in the pathogenesis of SSc vascular disease.

Objectives: In this study, we examined the expression levels of COL1, PCNA, PFKP, IP, EP2, IP, and PTGIS in SSc skin, the effects of Treprostinil (prostacyclin analog) on cell proliferation, TGFB1-induced collagen expression in SSc-vSMCs, PPARG expression and Yap nuclear translocation.

Methods: SSc and control skin biopsies were fixed and 10uM serial sections were cut for histological examination. vSMCs were isolated from involved skin and matched healthy subjects. The expression and distribution of collagen, PCNA, PFKP, IP, EP2, PTGIS, PPARG, and Yap were measured by immunohistochemical staining or immunofluorescent staining. Cell proliferation was measured by MTT assay. The mRNA expression levels were detected by qPCR.

Results: The protein expression levels of collagen, PCNA, PFKP, and EP2 were increased, while the expression levels of PTGIS and IP were decreased in vSMCs of SSc-skin, compared to the control. These results suggested that defective PGI2-IP signaling in SSc-vSMCs may contribute to vessel wall thickness and vascular fibrosis in SSc. Treprostinil inhibited vSMCs proliferation, COL1A1, and PFKP mRNA expression in SSc-vSMCs in a dose-dependent fashion. Treprostinil also inhibited TGFB1-induced COL1A1 mRNA expression in SSc-vSMCs via engagement of EP2. The PPARG expression was significantly increased in treprostinil-treated SSc-vSMCs. Treprostinil decreased the nuclear location of YAP which is induced by 10%FBS and TGFB1.

Conclusion: Defective PGI2-IP signaling in SSc-vSMCs is associated with enhanced expression of collagen, PCNA, and PFKP in SSc vessel walls. The antiproliferative and antifibrotic activity of treprostinil is mediated through the inhibition of YAP nuclear translocation and enhanced PPARG expression. YAP and PPARG might be promising therapeutic targets for the treatment of SSc-related vasculopathy.

