Therapeutic potential of the Nox1/4 inhibitor GKT137831 in Systemic Sclerosis

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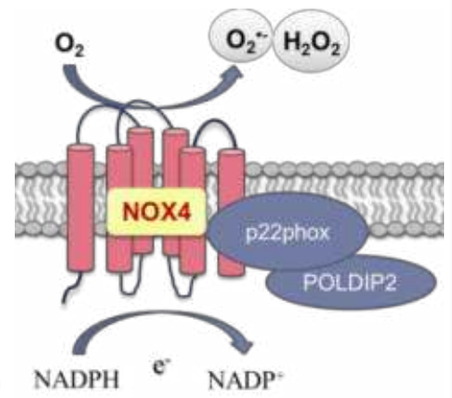
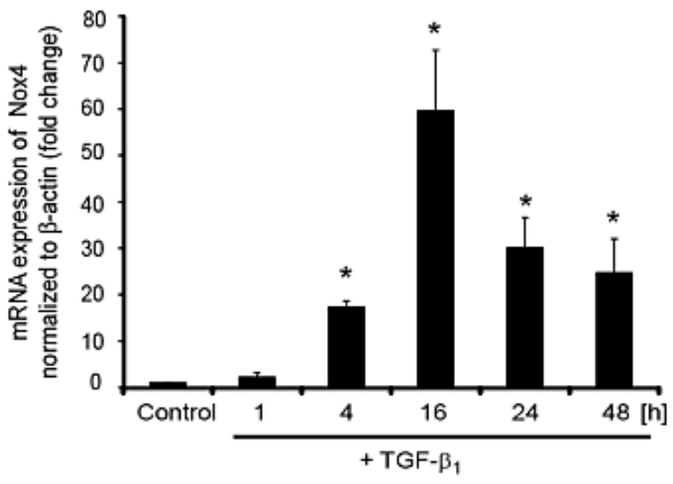
Introduction

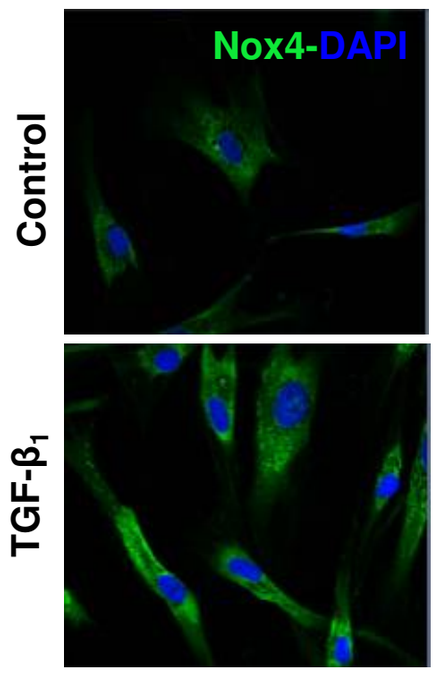
The pathogenesis of systemic sclerosis (SSc) is still incompletely understood. Transforming growth factor-β_1 (TGF-β_1)-mediated activation of fibroblasts and oxidative stress are crucially involved in the development of tissue fibrosis. Recently, we could show that Nox4, a member of the 7 nicotinamide adenine dinucleotide phosphate oxidase (Nox) family, is strongly upregulated by TGF-β_1 in normal human fibroblasts (HDFs). Genetic silencing of Nox4 as well as inhibition of Nox enzyme activity by the pan-Nox inhibitor diphenyleneiodonium neutralized this any toxicity in HDFs *in vitro*. Then, we examined whether GKeffect of TGF-β_1 (Dosoki et al. Exp. Dermatol. 2016). Here, we investigated the effect of GKT137831, a first-in-class small molecule dual-specific Nox1/4 inhibitor in HDFs *in vitro* as well as *in vivo* in experimentally induced skin fibrosis. First, we examined whether GKT137831 has T137831 can suppress TGF-β_1-mediated activation of HDFs *in vitro*. *In vivo* we employed the bleomycin (BLM) scleroderma mouse model to test whether GKT137831 can prevent experimentally induced skin fibrosis and is also capable to revert an already established skin fibrosis.



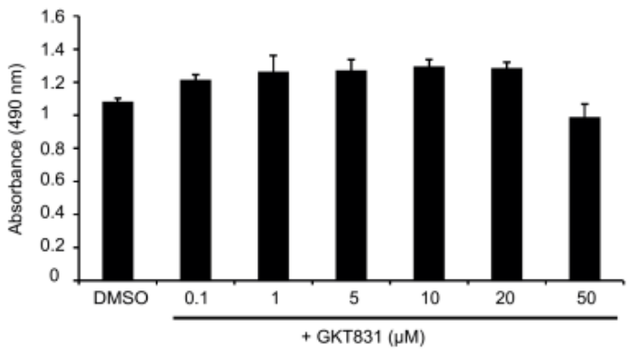
Results

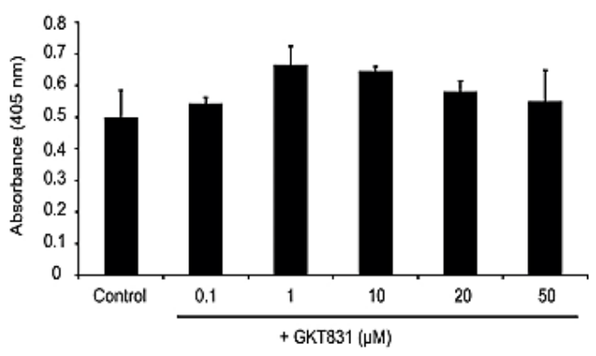
Nox4 is up-regulated by TGF-β_1 in HDF



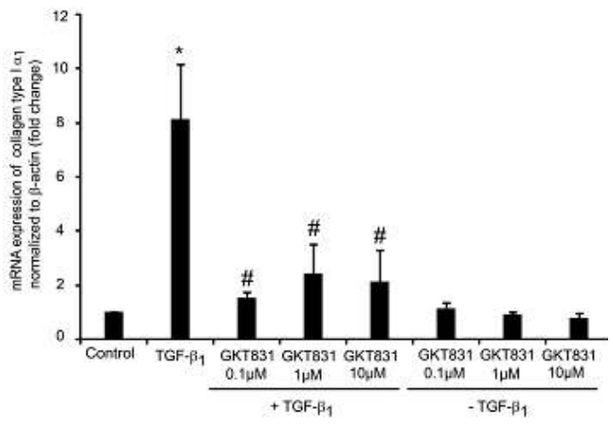


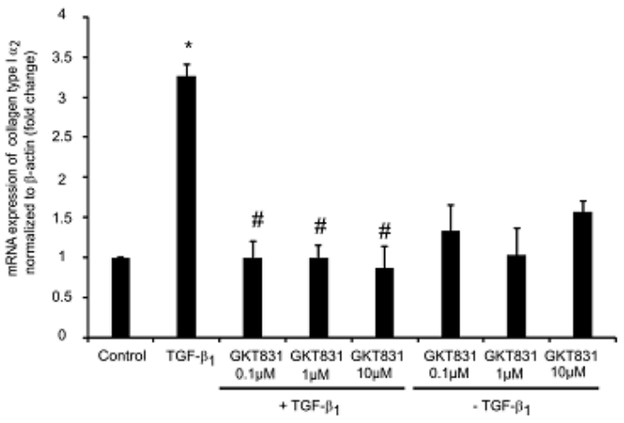
The Nox1/4 inhibitor GKT137831 does not affect cell viability and proliferation of HDFs

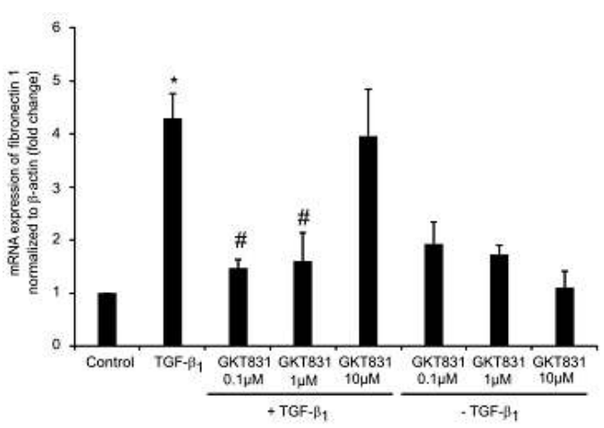


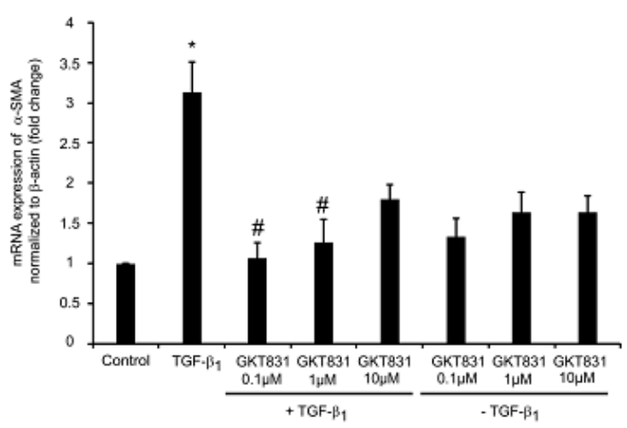


The Nox1/4 inhibitor GKT137831 reduces TGF-β_1-mediated upregulation of collagen type I, α-SMA and fibronectin 1

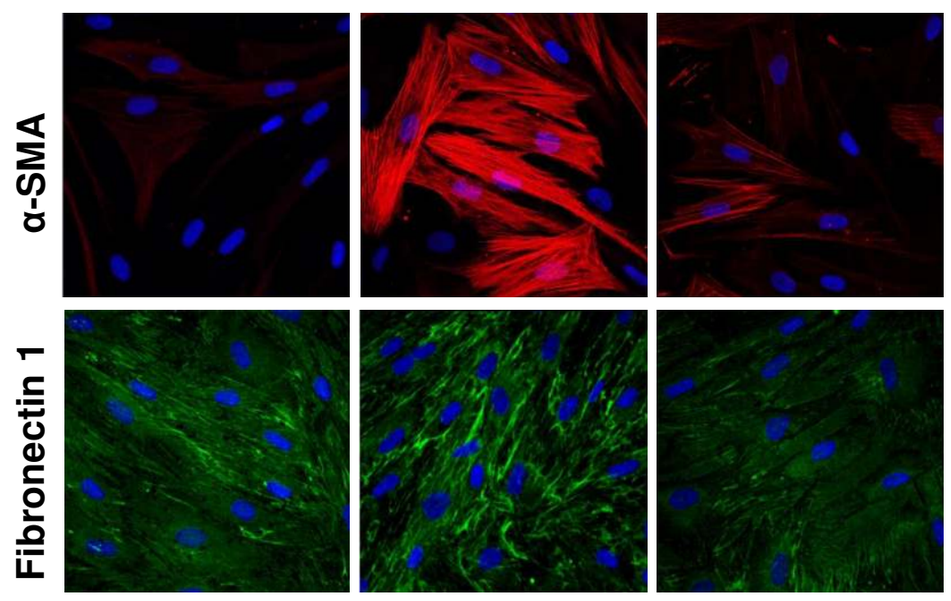




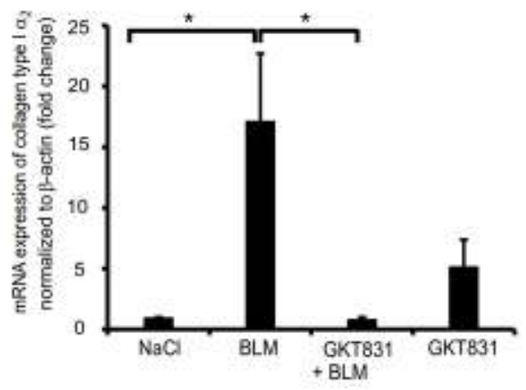


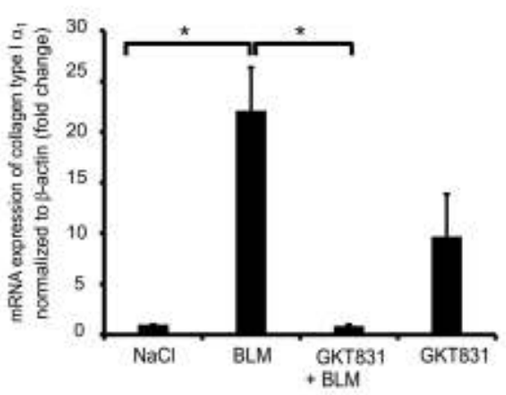


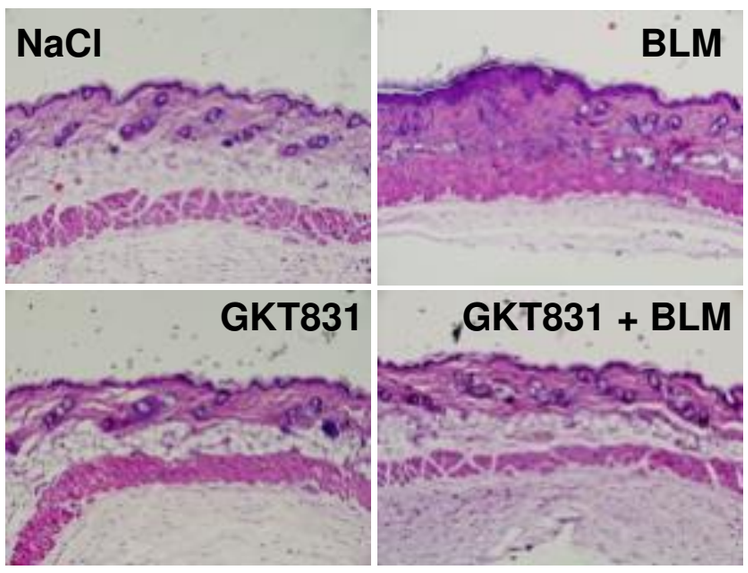
Control, TGF-β_1, TGF-β_1 + GKT137831

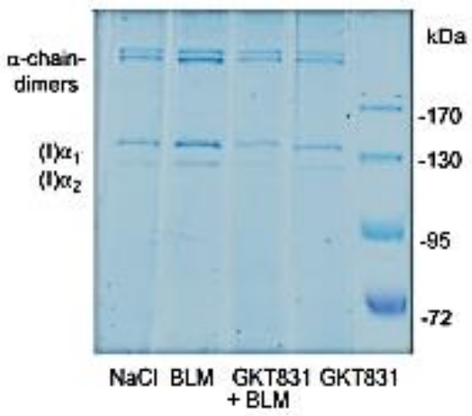


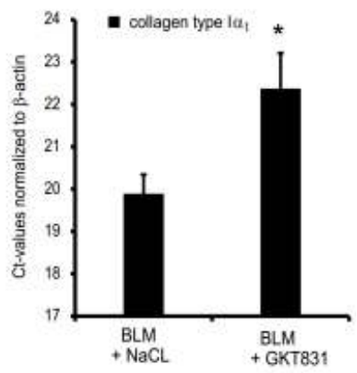
The Nox1/4 inhibitor GKT137831 attenuates bleomycin-induced skin fibrosis

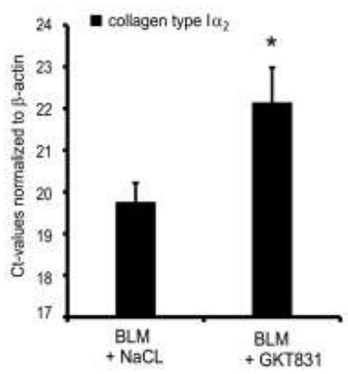


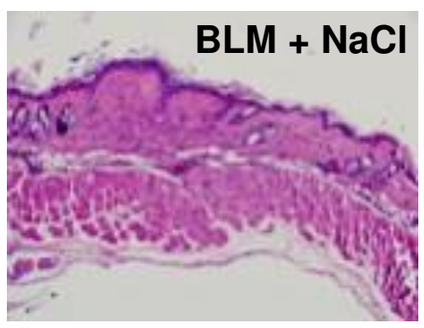


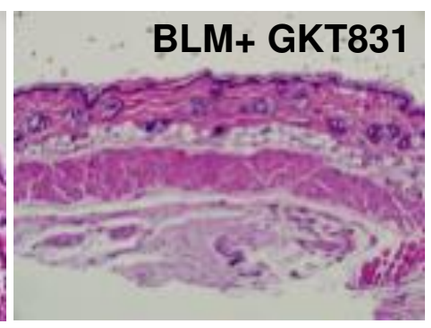


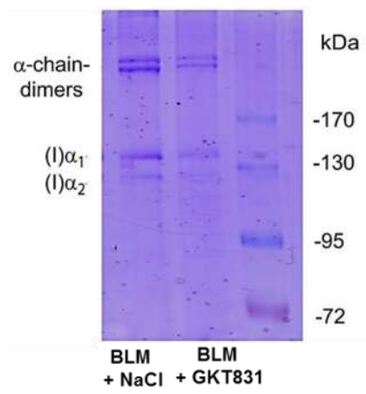












Conclusion

Our findings indicate that the Nox1/4 inhibitor GKT137831 could be a novel strategy for the treatment of fibrotic skin disease such as scleroderma

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