

MiR-200a inversely correlates with Hedgehog and TGF- β canonical/non-canonical trajectories to orchestrate the anti-fibrotic effect of Tadalafil in a bleomycin-induced pulmonary fibrosis model

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Abstract

Few reports have documented the ability of phosphodiesterase-5 inhibitors (PDE-5-Is) to ameliorate idiopathic pulmonary fibrosis (IPF) mainly by their anti-inflammatory/antioxidant capacities, without unveiling the possible molecular mechanisms involved. Because of the recent role of miR-200 family and Sonic Hedgehog (SHH) trajectory in IPF, we have studied their impact on the anti-fibrotic potential of tadalafil against bleomycin-induced pulmonary fibrosis. Animals were allocated into normal-control, bleomycin-fibrotic control, and bleomycin post-treated with tadalafil or dexamethasone, as the reference drug. On the molecular level, tadalafil has reverted the bleomycin effect on all the assessed parameters. Tadalafil upregulated the gene expression of miR-200a, but decreased the smoothed (SMO) and the transcription factors glioma-associated oncogene homolog (Gli-1, Gli-2), members of SHH pathway. Additionally, tadalafil ebbed transforming growth factor (TGF)- β 's canonical (SMAD-3/ α smooth muscle actin [SMA] and Snail), and non-canonical (p-Akt/p-Forkhead box O3 (FOXO3a) pathways. Besides, a strong negative correlation between miR-200a and the analyzed pathways was proved. The effect of tadalafil was further confirmed by the improved lung structure and the reduced Ashcroft score/collagen deposition. The results were comparable to that of dexamethasone. In conclusion, our study has highlighted the involvement of miR-200a in the anti-fibrotic effect of tadalafil with the inhibition of SHH hub and the pro-fibrotic pathways (TGF- β 's SMAD-3/SMA, Snail and p-AKT/p-FOXO3a). Potential anti-fibrotic effect of tadalafil. Modulation of miR200a/SHH/canonical and non-canonical TGF- β trajectories. β 's stimulatory effect; β 's inhibitory effect.

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