AMPK-FOXO3a pathway inhibits fibroblast-myofibroblast differentiation by activating autophagy during pulmonary fibrosis

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Background: Fibroblast to myofibroblast differentiation (FMD) is an important feature of pulmonary fibrosis (PF), which promotes collagen deposition and leads to the destruction of lung tissue structure. Recent studies suggested that autophagy is involved in the progression of PF. However, it remains elusive whether autophagy can inhibit FMD during the development of PF. In addition, AMPK-FOXO3a pathway can induce autophagy in many tissue, but no research has shown this pathway participate in the pathogenesis of PF.

Methods: In vivo, we developed PF model in SD rats by intracheal administration of bleomycin (BLM), and metformin was gavaged from second day. The protein expression of autophagy and myofibroblast markers including lc3, p62, α-SMA were detected by western blot or immunohistochemical. In vitro, human embryonic lung fibroblasts (HELF) were stimulated with TGF-β1 and metformin. Furthermore, transfected with FOXO3a siRNA and conducted with the inhibitor of autophagy to determine the effect of AMPK-FOXO3a pathway to FMD.

Results: In vivo, we found that FMD was more severity in PF rats, and the expression of AMPK and FOXO3a were significantly decreased with a lowered autophagy level. Meanwhile, treatment with metformin attenuated fibrosis induced by BLM. In vitro, metformin treatment attenuated FMD induced by TGF-β1 accompanied by high level of autophagy, and increased expression of AMPK, FOXO3a in human embryonic lung fibroblasts. Inversely, silenced FOXO3a by siRNA aggravated FMD once again. Interestingly, when conducted with inhibitor of autophagy in fibroblast, metformin treatment could not decreased FMD.

Conclusion: AMPK-FOXO3a pathway alleviates FMD during PF by raising the level of autophagy. These findings promote the exploration of the pathogenesis of PF and may provide a new insight for treatment of PF.

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