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Title: TSC1/mTOR pathway promotes hypoxia-induced pulmonary hypertension in mice

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Body: Background: Chronic hypoxia is a key trigger of pulmonary vascular remodeling in pulmonary hypertension (PH). The mammalian target of rapamycin (mTOR) is involved in cell proliferation, which is negatively regulated by Tuberous sclerosis complex 1(TSC1). However, whether TSC1/mTOR pathway is involved in hypoxia-induced PH is still unknown. Objective: To find whether TSC1/mTOR pathway is involved in PH and provide a target for its therapy. Methods: Endothelial cell-specific mutation of TSC1 in mice (Tek-cre(+)/TSC1$^{fx/+}$ and Tek-cre(-)/TSC1$^{fx/+}$) (provided by prof. Kai-feng Xu) were used. The mice were exposed to either hypoxia(10% O_2) or normoxia (21% O_2), then the right ventricular systolic pressure(RVSP), and index of right ventricular hypertrophy(RVHI) were measured. Histological measurement was used to estimate the distal vascular remodeling. Western blot was used to detect the change of protein expression in mice lungs. Results: Those two genotypic mice under normoxia showed no differences. After hypoxia, RVSP and RVHI of those two genotypic mice was gradually increased, but Tek-cre(+)/TSC1$^{fx/+}$ mice were higher after 3 weeks (RVSP: 22.79±0.31 vs. 19.95±0.97mmHg, $p<0.05$; 0.32±0.01 vs. 0.25±0.02, $p<0.05$). The small pulmonary arteries of both Tek-cre(+)/TSC1$^{fx/+}$ and Tek-cre(-)/TSC1$^{fx/+}$ showed progressive medial thicken under hypoxia, but the former was more obvious. The expression of phosphorylation of S6 (biomarker of mTOR) gradually increased in lungs of these two genotypic mice exposed to hypoxia in the first 2 weeks, then decreased. And Tek-cre(+)/TSC1$^{fx/+}$ mice showed higher amounts. Conclusion: TSC1/mTOR pathway can promote hypoxia-induced PH in mice, which provides a novel target for PH therapy.