Identification of Emetine as a Novel Therapeutic Agent for Pulmonary Hypertension in Rats -High-throughput Screening of 5,562 Compounds-

（書式１８）論文博士

学　位　論　文　要　約

博士論文題目　Identification of Emetine as a Novel Therapeutic Agent for Pulmonary Hypertension in Rats-High-throughput Screening of 5,562 Compounds-

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Pulmonary arterial hypertension (PAH) is a fatal disease characterized by enhanced proliferation and reduced apoptosis of pulmonary arterial smooth muscle cells (PASMCs). Here, we target hyperproliferative feature of PASMC in patients with PAH to discover a novel drug that inhibits its proliferation. To discover a novel compound for PAH patients from the original 5,562 compounds, we performed stepwise screenings for 5,562 compounds from original library. In the first screening, we performed MTT assay for each compound (5 μM/L) and found 80 compounds that effectively inhibited proliferation compared with controls (>20%). In the second screening, we performed the repeatability assay and the counter assay to exclude the compounds with cell toxicity. In the third screening, we performed a concentration-dependent assay and finally found that emetine inhibits PAH-PASMCs proliferation without any toxicity in normal PASMCs. Interestingly, emetine significantly reduced protein levels of hypoxia-inducible factors (HIF-1α and HIF-2α) and downstream pyruvate dehydrogenase kinase 1. Moreover, emetine significantly reduced the protein levels of RhoA, Rho-kinase (ROCK1 and ROCK2), and their downstream cyclophilin A and basigin in PAH-PASMCs. Consistently, emetine treatment significantly reduced the secretion of cytokines/chemokines and growth factors from PAH-PASMCs. Next, we performed functional tests for emetine in vivo. Six-week-old male SD rats were used for the two experimental PH models; monocrotaline-induced PH model and SU5416/hypoxia-induced PH model. Importantly, emetine treatment as 0.05 mg/kg/day which is twenty times much lower than clinical dose in human ameliorated pulmonary hypertension in two experimental rat models by reducing right ventricular systolic pressure (RVSP), right ventricular hypertrophy (RVH), and pulmonary artery (PA) remodeling compared with vehicle controls. Moreover, emetine treatment reduced inflammatory cytokines/chemokines and growth factors in serum compared with vehicles controls. Finally, emetine treatment improved RV functions and enhanced exercise capacity compared with vehicle controls. In conclusion, by using high-throughput screening, we identified emetine that reduces excessive proliferation of PAH-PASMCs and ameliorates pulmonary arterial hypertension, is a natural alkaloid extracted from *Psychotria ipecacuanha*, which has been traditionally used to treat cough and amebiasis.