Transgelin-2 as a therapeutic target for asthmatic pulmonary resistance

With the support by the National Natural Science Foundation of China, the research team directed by Prof. Yang YongQing (杨永清) at Shanghai University of Traditional Chinese Medicine, reported that transgelin-2 is a therapeutic target for asthmatic pulmonary resistance and its agonist can relax airway smooth muscle cells to provide therapeutic advantages for asthma, which was published in *Science Translational Medicine* (2018, 10(427): eaam8604) and has been selected as the cover story.

More than half of asthmatic patients do not receive adequate control with currently available treatments. Therefore, there is a clinical need for new bronchodilator drugs in asthma. Based on their previous report that metallothionein-2 (MT-2) was one of the differentially expressed gene in asthma treated by acupuncture, this study reports for the first that inhibition of MT-2 protein expression in lung tissues causes the increase of pulmonary resistance. On the contrary, giving recombinant MT-2 protein is more effective than β_2-agonists in reducing pulmonary resistance in rodent asthma models, alleviating tension in tracheal spirals, and relaxing airway smooth muscle cells (ASMC). MT-2 relaxes ASMC via transgelin-2 (TG2) and induces dephosphorylation of myosin phosphatase target subunit 1 (MYPT1). A small compound named TSG12 was identified as a non-toxic, specific TG2-agonist that relaxes ASMC and reduces asthmatic pulmonary resistance via TG2. *In vivo*, TSG12 reduces pulmonary resistance in both ovalbumin and house dust mite-induced asthma in mice. TSG12 induces RhoA phosphorylation, thereby inactivating the RhoA-ROCK-MYPT1-MLC pathway and causing ASMC relaxation. TSG12 is more effective than β_2-agonists in relaxing human ASMC and pulmonary resistance with potential clinical advantages. These results suggest that transgelin-2 agonists could be a promising therapeutic approach for treating asthma.

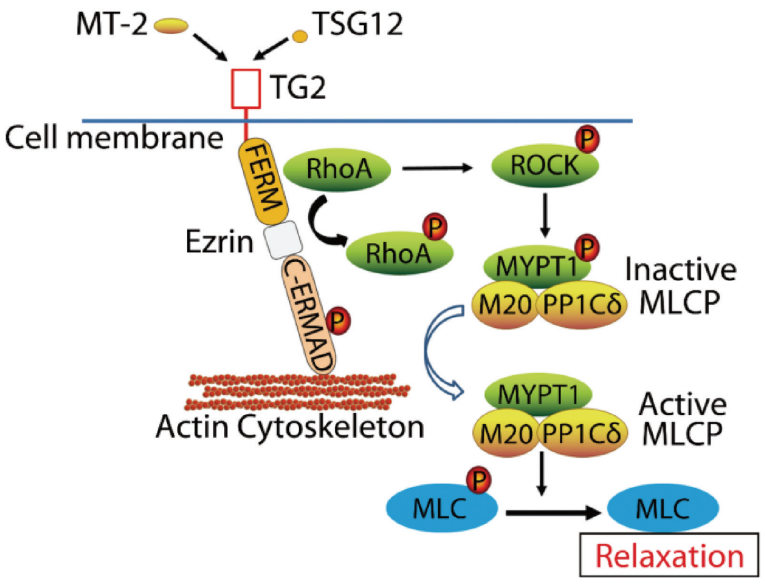

Figure Proposed mechanism of ASMC relaxation induced by transgelin-2. MT-2 or TSG12 activates TG2 to bind ezrin. TG2 activation induces RhoA phosphorylation serine-188. This phosphorylation inhibits RhoA and prevents the phosphorylations of ROCK and its substrate myosin phosphatase target subunit 1 (MYPT1). The myosin light chain phosphatase (MLCP) complex becomes activated to dephosphorylate myosin light chain (MLC) and induces ASMC relaxation.