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Sildenafil increases connexin 40 in smooth muscle cells through activation of BMP pathways in pulmonary arterial hypertension

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Background: Pulmonary arterial hypertension (PAH) is a cardiovascular disorder associated with enhanced proliferation and suppressed apoptosis of pulmonary arterial smooth muscle cells (PASMCs). The sildenafil can regulate the Connexin (Cx) 43 in the PASMCs and thus inhibit the PASMCs proliferation and the remodeling of pulmonary arterial. However, how sildenafil exert regulation in the Cx40 in the PASMCs in PAH remains unclear.

Methods & Results: Using the rat PAH model induced by the monocrotaline, we demonstrated that the Cx40 in the PASMCs is down-regulated in the PAH. The sildenafil promotes the up-regulation of Cx40 in the PASMCs via bone morphogenetic protein (BMP) signaling, accompanied by an anti-proliferative response in PASMCs. Inhibition of the BMP axis reverses the up-regulation of Cx40 and anti-proliferation of the sildenafil in these cells. In monocrotaline-induced PAH rat models, which display reduced levels of BMP signaling, this study further indicates that the BMP-Cx40 axis is activated in lungs following the sildenafil treatment. Furthermore, we also find in vitro that sildenafil increases the Cx40 expression of PASMCs isolated from MCT-PAH rats and inhibit the proliferation of these cells. These phenomenon are reversed by LDN-193189, the antagonist of type II receptor for bone morphogenetic protein (BMP2) treatment, providing strong evidence for the protect effect of sildenafil and the BMP-Cx40 axis involvement.

Conclusions: Taken together, these data suggest the sildenafil activate BMP-Cx40 signaling in the PAH. This axis may be a potential therapeutic target in PAH.

Biography

Lei Yang completed his Doctorate degree of Pediatrics from Nanjing Medical University. After his graduation, he was engaged in clinical and research work of Congenital Heart Disease in Nanjing Children's Hospital affiliated to Nanjing Medical University. So far, he has chaired and completed development of science and technology of Nanjing Medical University foundation project. His study has been based on the development mechanism of the occurrence, clinical diagnosis and treatment in children with congenital heart disease. He has published 7 SCI papers. As the first inventor, he obtained 2 national patents (authorized), as the second inventor; he obtained 1 national patent (authorized).

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