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Piezo1, a novel therapeutic target to treat pulmonary arterial hypertension

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Introduction

Pulmonary arterial hypertension (PAH) is a life-threatening disorder characterized by Abrelevated mean pulmonary arterial pressure (mPAP >20 mmHg) as a consequence of enhanced pulmonary vascular resistance (PVR) (Simonneau et al., 2019). Pulmonary artery vasoconstriction and vascular remodeling greatly contribute to a sustained elevation of PVR and pulmonary arterial pressure (PAP) in patients with PAH. Abnormal upregulation of cytoplasmic Ca2+ in pulmonary artery smooth muscle cells plays a central role. However, calcium channel blocker (CCB) is only effective in 10% of patients with a positive acute vascular response and it is rapidly becoming resistant to treatment (Galie et al., 2015). The main pharmacological effect of CCB is the inhibition of L-type voltage-dependent calcium channels (VDCC), thus inhibiting receptor-operated Ca2+ channels (ROCC) which mainly regulates Ca2+ influx and consequently blocks the process of vasoconstriction (Ng and Gurney, 2001).

It is known that the main components of store-operated calcium channel (SOCC) are the members of the transient receptor potential channel (TRPC) family (Somlyo and Somlyo, Nature, 1994, 372, 231–236; Birnbaumer et al., Proc Natl Acad Sci United States, 1996, 93, 15,195–15202; Zhu et al., Cell, 1996, 85, 661–671; Zitt et al., Neuron, 1996, 16, 1,189–1,196) and pulmonary artery smooth muscle cell (PASMC) mainly expressed TRPC1, TRPC2, TRPC4, TRPC5, and TRPC6 (Golovina et al., Am J Physiol Heart Circ Physiol, 2001, 280, H746–755) . A mountain of studies (Golovina et al., Am J Physiol Heart Circ Physiol, 2001, 280, H746–755; Sweeney et al., Am J Physiol Lung Cell Mol Physiol, 2002, 283, L144–155; Fantozzi et al., Am J Physiol Lung Cell Mol Physiol, 2003, 285, L1233–1,245) has suggested that transient receptor potential channel played an important role in the development of PH, but few of them can be used as an effective therapeutic target. We find it difficult to target TRPC as a treatment target because of its wide implication. Du et al. (Du et al., FASEB J, 2014, 28, 4677–4685) described that TRPC1 can act as a component that senses shear stress.

It is generally recognized that shear stress, one of the most significant intravascular mechanics, plays a significant role in the contraction and remodeling of the vasculature. Piezo1 is a mechanosensitive, non-selective cationic ion channel protein. In specific, the Piezo channels are activated by shear stress in local blood flow and by cell membrane stretch (Douguet et al., 2019). We, therefore, suggest that Piezo1 is the initiating factor in the disturbance of Ca^{2+} homeostasis in PASMC in some types of PAH, for example, chronic thromboembolic pulmonary hypertension (CTEPH) and congenital heart disease-associated PAH. The primary roles of Piezo1 in vascular mechanical transduction have been identified as sensing blood flow shear stress and fostering vascular development (Li

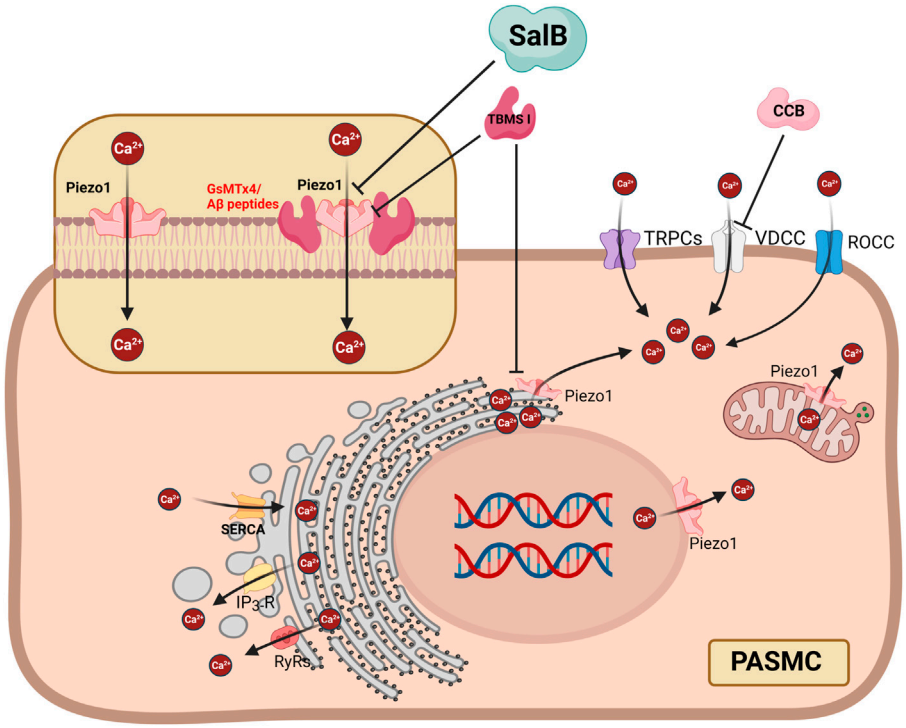

FIGURE 1
Proposed mechanisms showing that inhibition of Piezo1 in PASMC can suppress Ca^{2+} influx and release from subcellular organelles, as well as Ca^{2+} flow mediated by other Ca^{2+} channels. SalB can inhibit extracellular Ca^{2+} influx through the PM localized Piezo1 but not subcellular organelles. GsMTx4 and Aβ peptides inhibit Piezo1 by changing the structure of the membrane. TBSM I suppresses PM localized Piezo1 and subcellular organelles localized Piezo1. ER = Endoplasmic Reticulum; IP3R = inositol 1,4,5-trisphosphate receptors; PASMC = pulmonary artery smooth muscle cell; PM = plasma membrane; ROCC = receptor-operated Ca^{2+} channels; RyRs = ryanodine receptors; SalB = Salvianolic Acid B; SERCA = sarcoplasmic reticulum Ca [2+]-ATPase; SR = Sarcoplasmic Reticulum; VDCC = voltage-dependent calcium channels. The fiure is created with BioRender.com.

et al., 2014). Piezo1 is localized at the subcellular organelles, including the endoplasmic reticulum (ER)/sarcoplasmic reticulum (SR), nucleus, and mitochondria; as well as the plasma membrane. Activation of Piezo1 increased intracellular free calcium concentration in a SOCE-independent manner (Liao et al., 2021) and over-expression of Piezo1 improved cell migratory velocity, showing Piezo1 involvement in cell motility (Maneshi et al., 2018). Additionally, it has been shown that effective knockdown of Piezo1 attenuated the FBS-induced proliferation of human PASMC (Maneshi et al., 2018) and inhibited the FBS-induced proliferation of human PASMC (Liao et al., 2021). Also, previous study (Chen et al., 2022)have shown that Piezo1 is required for pulmonary artery smooth muscle cell proliferation. Expression of Piezo1 is increased in the pulmonary artery endothelial cells of patients with idiopathic pulmonary artery hypertension and experimental PH (Wang et al., 2021) . In summary, Piezo1 expression is increased in both smooth muscle cells and endothelial cells of patients with PH and plays a pathological role.

Recently, some molecules have been found to inhibit Piezo1, some of which are derived from herbal ingredients, creating opportunities for the clinical application of Piezo1 as a therapeutic target. Salvia miltiorrhiza produces salvianolic acid B (SalB), a significant bioactive molecule that is water soluble. SalB shows a preference for Piezo1 channels and reduces the current caused by mechanical stimulation and Yoda1 stimulation, suggesting that it may have an impact on the vascular mechanical transduction in Piezo1 channels (Pan et al., 2022). A possible mechanism for the inhibition of Piezo1 by SalB might be that it competitively inhibits the action of Yoda1[18]. A specific Piezo1 blocker is the peptide GsMTx4, which was extracted from the venom of the spider Grammostola spatulata (Suchyna et al., 2000). According to biophysical research, Piezo channels may be able to directly detect mechanical force when a lipid membrane is perturbed (Cox et al., 2016). Amphipathic medicines, such as Aβ-peptides, modify membrane mechanics by changing the structure of the membrane (Williams and Serpell, 2011). Mohammad M. Maneshi and his colleagues (Maneshi et al., 2018) proved that enantiomeric Aβ peptides inhibit the fluid shear stress response of Piezo1, which inhibits Piezo1 from another possible mechanism by altering membrane structure and mechanics. The Chinese herb Bolbostemma paniculatum (Maxim) Franquet (Cucurbitaceae), often known as "Tu Bei Mu," has a triterpenoid saponin called tubeimoside I (TBMS I) (Tang et al., 2015), which stands out as an efficient inhibitor of the Yoda1-response with selectivity for the Piezo1 channel (Liu et al., 2020) Figure 1. Based on the above

studies, Piezo1 is promising as a target for the treatment of PAH. Piezo1 may act as an adaptive compensator in the initial stages of PAH, but Piezo1 acts as a pressure-sensing sensor, and changes in intravascular shear stress activate Piezo1, thereby disrupting calcium homeostasis. Therefore, Piezo1 may be a potential treatment target for PAH. Whereas further experiments are needed to confirm at which stage of PAH the intervention will have a positive effect.

Author contributions

YC designed the study. HY, XL, and YX collected the literature drafted the manuscript.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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