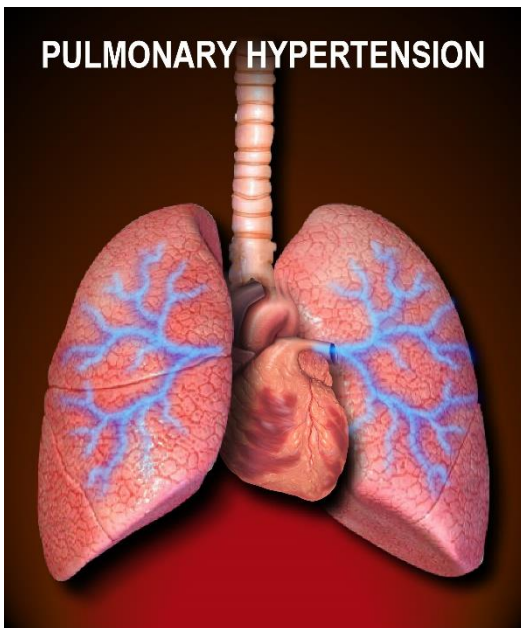


Project 2: Piezo1 in arterial remodeling



The pulmonary circulation is a low-pressure low resistance system allowing the whole cardiac output to cross the lung (85-87). **Pulmonary hypertension (PH) is characterized by increased pulmonary artery (PA) pressure and resistance, which negatively impacts the right ventricular (RV) function because of enhanced afterload.** It may appear as idiopathic pulmonary arterial hypertension but may also be associated with a variety of conditions, including chronic hypoxemia (88). In PH, increased arterial reactivity and structural remodeling occur with a thickening of the medial layer of small muscular PAs (85-87). PA SMCs hypertrophy is a characteristic pathological feature of PH that involves muscularized arteries (ranging between 70 and 500 μm in diameter), and precapillary vessels (below 70 μm in diameter) (85-87). The mechanisms underlying the thickening of the pulmonary vascular medial layer are also linked to enhanced SMCs proliferation (hyperplasia). Several arguments point to an important role for mechanical stress in PH. First, PA remodeling is associated with a prolonged vasoconstriction of muscular PAs, as occurring during hypoxemia at high altitude or secondary to chronic hypoxic pulmonary diseases (85-87). Second, patients with heart dysfunctions leading to an increase in PA pressure also develop pathological remodeling of the pulmonary vessels (85-87). Third, stretch stimulates hypertrophy and hyperplasia of cultured PA SMCs (89, 90).

Conventional treatments include vasodilators or anticoagulation to alleviate the symptoms (88). However, no curative treatment allowing a reversion of PA remodeling is yet available. Thus, a better understanding of the molecular basis of PA remodeling is urgently needed to identify novel therapeutic options. **In the present project, we postulate that mechanical stress is a major contributor of medial vascular remodeling in PH.** We are currently exploring the functional role of Piezo1 in PA SMCs hypertrophy and hyperplasia associated with PH.

The general objective of this program is to decipher the role of Piezo1 in PH. Our specific aims are: 1) to establish the link between Piezo1 and MS ion channels in PA SMCs; 2) to map Piezo1 activation in PA SMCs *in vivo* upon PH; 3) to determine the role of SMCs Piezo1 in PA remodeling associated with PH; 4) to identify the signaling pathways downstream of Piezo1 opening in PA SMCs. Our strategy combines studies with PA SMCs from PH and control patients (collaboration with Serge Adnot, Institut Mondor de Recherche Biomédicale, Créteil, France), together with SMCs specific Piezo1 knock-out (KO) (*smMHC Cre (ERT2) Piezo1 del/lox*) generated by our group (4) and Piezo1 knock-in (KI) GOF mouse models (collaboration with Ardem Patapoutian, TSRI, La Jolla, CA, USA). In brief, PH will be assessed based on determination of right ventricular (RV) pressure and assessment of RV hypertrophy (Fulton index). Complementary studies will assess (1) the growth rate of cultured PA SMCs derived from Piezo1 KO/KI mice compared to control mice, both in normoxic or hypoxic conditions; (2) the role of Piezo1 in PA SMCs calcium signaling and reactivity of isolated intrapulmonary arteries.

Ultimately our findings are anticipated to pave the way for the identification of novel therapeutic opportunities to fight PH, targeting Piezo1 in PA SMCs.

References cited:

4. **K. Retailliau *et al.*, *Cell Rep* 13, 1161 (2015).**
85. **R. M. Tuder, *Semin Respir Crit Care Med* 30, 376 (Aug, 2009).**
86. **M. Rabinovitch, *J Clin Invest* 118, 2372 (Jul, 2008).**
87. **K. R. Stenmark, B. Meyrick, N. Galie, W. J. Mooi, I. F. McMurtry, *Am J Physiol Lung Cell Mol Physiol* 297, L1013 (Dec, 2009).**
88. **F. Soubrier *et al.*, *J Am Coll Cardiol* 62, D13 (Dec 24, 2013).**
89. **K. G. Birukov, *Antioxid Redox Signal* 11, 1651 (Jul, 2009).**
90. **A. S. Dick *et al.*, *Free Radic Biol Med* 61, 310 (Aug, 2013).**