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Altering Smooth Muscle Cell (SMC) Identification and Differentiation States to Understand the Role of SMC in Normal and Pulmonary Arterial Hypertension Phases

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Pulmonary arterial hypertension (PAH) is a debilitating and often fatal disease associated with reduced BMPR2signalling. Limited human tissue is available for study and usually only from patients with end-stage disease, making it difficult to understand how PAH is established and progresses. Furthermore, BMPR2 knockout mouse models are unable to recapitulate the full repertoire of phenotypes observed in humans. We therefore require alternative human models of PAH. We derived iPSCs from patients with BMPR2 mutations and used CRISPR-Cas9 gene editing to introduce two specific BMPR2 mutations into control iPSCs with no history of PAH. Using these cells, we generated the first human iPSC model of PAH involving the analysis of lineage-specific iPSC-derived pulmonary artery smooth muscle which recapitulate several PAH-associated phenotypes. These unique models with isogenic backgrounds revealed that a single BMPR2 mutation is sufficient to cause some PAH-associated phenotypes, but that other factors are necessary to enhance BMPR2-associated phenotypes in vivo. We next defined ways to control the transition between normal and diseased states in the model. For example, we showed that acquisition of the mitochondrial hyperpolarisation phenotype is enhanced by inflammatory signalling and requires an interaction between BMPR2 mutations and environmental stimuli provided by exposure to serum factors over time. We are now using the iPSC model to elucidate and track the mechanisms regulating disease initiation and progression in a way not possible before, and for validating therapeutic approaches to treat PAH.

Biography

Ayat J Alansari is earned Master's degree at the age of 25 from Thomas Jefferson University in the U.S.A. Currently, I am a senior laboratory specialist at Alnoor Specialist Hospital in Saudi Arabia. I am a Ph.D. candidate studying cardiovascular regenerative medicine and stem cell biology at the University of East Anglia, UK.