



CHINESE-AMERICAN LUNG ASSOCIATION



CALA Happy Friday Seminar

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Zoom: 82407021221 (Password: 654321)

Reduced Notch1 Cleavage Promotes the Development of Pulmonary Hypertension



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Bio: Dr. Pang obtained her MD and PhD in China and completed her postdoctoral training with Dr. William Chilian and Dr. Bradford Berk who are the pioneers of cardiovascular field. Dr. Pang's research is mainly focused on angiogenesis and vascular remodeling, which are critical events for tissue development and repair, and are associated with many diseases (e.g. Pulmonary artery hypertension, Bronchopulmonary dysplasia, ischemic cardiomyopathy, retinopathy and tumor growth). The long-term goal of Dr. Pang's lab is to identify the essential targets that regulate angiogenesis and vascular remodeling under physiological and pathological conditions. In last 15 years, her group revealed several novel mechanisms on angiogenesis and vascular remodeling during organ development and vascular diseases, such as GIT1 mediated GPCR signaling and Dll4-Notch signaling. Her group recently developed a novel pipeline, called "Vessel Tech", for analyzing vascular characteristics using machine learning methods, which provides a powerful tool for vascular biologists. Dr. Pang's contributions in cardiovascular research fields have been evidenced by being the winner of the AHA Cournand and Comroe Young Investigator Award, AHA SDG award and AHA IPA awards and total 48 publications including *Circulation*, *Cell Report*, *Hypertension* et al. She has served as a reviewer of the cardiovascular-related journals, as well as the reviewer of NHLBI, Department of Defense and AHA.

Abstract: Clinical trials of Dll4 (Delta-like 4) neutralizing antibodies (Dll4nAbs) in cancer patients are ongoing. Surprisingly, pulmonary hypertension (PH) occurs in 14% to 18% of patients treated with Dll4nAbs, but the mechanisms have not been studied. Here, PH progression was measured in mice treated with Dll4nAbs. We detected Notch signaling in lung tissues and analyzed pulmonary vascular permeability and inflammation. Notch target gene array was performed on adult human pulmonary microvascular endothelial cells (ECs) after inhibiting Notch cleavage. Similar mechanisms were studied in PH mouse models and pulmonary arterial hypertension patients. The rescue effects of constitutively activated Notch1 *in vivo* were also measured. We observed that Dll4nAbs induced PH in mice as indicated by significantly increased right ventricular systolic pressure, as well as pulmonary vascular and right ventricular remodeling. Mechanistically, Dll4nAbs inhibited Notch1 cleavage and subsequently impaired lung endothelial barrier function and increased immune cell infiltration in vessel walls. *In vitro*, Notch targeted genes' expression related to cell growth and inflammation was decreased in human pulmonary microvascular ECs after the Notch1 inactivation. In lungs of PH mouse models and pulmonary arterial hypertension patients, Notch1 cleavage was inhibited. Consistently, EC cell-cell junction was leaky, and immune cell infiltration increased in PH mouse models. Overexpression activated Notch1-attenuated progression of PH in mice. In conclusion, Dll4nAbs led to PH development in mice by impaired EC barrier function and increased immune cell infiltration through inhibition of Notch1 cleavage in lung ECs. Reduced Notch1 cleavage in lung ECs could be an underlying mechanism of PH pathogenesis.