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Signaling and remodeling processes in the pulmonary circulation

Andrew Peacock from the Scottish Pulmonary Vascular Unit has nicely reviewed the major molecular mediators, known to be involved in pathological features of pulmonary artery hypertension: Thickening of media and adventitia; intimal proliferation; plexiform lesions and in situ thrombosis. Among the molecules, acting on endothelial cells or fibroblasts are the endothelins; bone morphogenic proteins (BMP); TGFbeta; vascular endothelial growth factor; various additional growth factors such as epithelial growth factor, platelet derived growth factors and of course Serotonin (5-HT). These mediators are acting according to genetic factors (susceptibility genes, modifying genes), environmental exposure (e.g. anorectic drugs, HHV-8,...) and associated diseases. Among the genetic factors, major progresses have been done on the recognition of BMP receptor 2 (BMPR II) mutations in familial or idiopathic pulmonary hypertension with 55 % mutation incidence in familial cases and 26 % BMPR II mutation in sporadic cases. BMPR II has been shown to work by a "smad" dependent pathway and a "smad" independent pathway (p38 MAPK), leading to major hope of new therapeutic interventions. p38 inhibitors are shown indeed to abrogate hypoxia stimulated proliferation of human pulmonary cells. Serotonin signalling pathways, involved in the regulation of pulmonary artery smooth muscle cell proliferation, are getting better identified with involvement of transcription signals such as ERK. The Serotonin transporter (5-HTT) is a key determinant of pulmonary vascular remodelling. It is expressed in response to hypoxia and is overexpressed in primary pulmonary hypertension (PPH). LL homozygote for 5-HTT is shown to be not only increased in PPH, but also in secondary PH (COPD). Antagonists of 5-HT and 5-HTT inhibitors are able to abrogate rat pulmonary vascular remodelling in response to hypoxia. Thus, these inhibitors may soon be additional therapeutic approaches to endothelin receptor antagonists; phosphodiesterase inhibitors; prostacyclins; K⁺ channel activators or statins.

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Chairman of the session "Epidemiology and genetics of pulmonary hypertension"