Abstract: P570

Pharmacological activation of nuclear receptor Nur77 decreases endothelial cell dysfunction and reduces experimental pulmonary hypertension

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Background: Pulmonary arterial hypertension (PAH) is a deadly disease characterized by abnormal remodelling of pulmonary vessels that lead to progressive increase in pulmonary artery pressure, right heart failure, and a high mortality rate. Pulmonary artery remodelling is associated with dysfunctional endothelial cells (ECs) in small lung arteries. Nuclear receptor Nur77 plays a critical role in inflammation and vascular disease. Activation of Nur77 attenuates inflammation and proliferation of vascular cells including ECs in vitro and in vivo.

Purpose/Aim: To investigate the role of Nur77 in vascular remodelling and right ventricle dysfunction in PAH.

Methods and Results: The expression of Nur77 is significantly decreased in lungs and ECs of both idiopathic and hereditary PAH patients as demonstrated by qPCR. Ectopic expression of Nur77 resulted in augmented expression of BMPR2 and ID1, which are impaired in PAH ECs. Furthermore, overexpression of Nur77 decreased expression of pro-inflammatory cytokines though inhibition of NFkB. Nur77 reduces proliferation of PAH ECs through attenuating CyclinD1 expression. 6-Mercaptopurine (6-MP), a known agonist of Nur77 decreases proliferation and inflammation of PAH ECs. Consistent with this, 6-MP displayed a beneficial effect on the lung remodelling through inhibition of proliferation of ECs and SMCs, and reduction of inflammation in vivo (Sugen Hypoxia rat model). Importantly, 6-MP improved impaired cardiac function compared to control group.

Conclusions: Our data indicate that Nur77 is a novel critical modulator in PAH through increasing BMP signalling while decreasing proliferation and inflammation. Therefore, activation of Nur77 via 6-MP might be useful for the treatment of PAH.