PSGR olfactory receptor: A new potential target in pulmonary arterial hypertension

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AUTHOR INFORMATION

Audrey Courboulain¹, Marceau Quatredeniérs¹, Guenhaél Sanz³, Sandra Breuils-Bonnet², Matthieu Vocelle¹, Mathilde Lafond¹, Frédéric Perros¹, Sébastien Bonnet², Edit Pajot-Augy³, Marc Humbert^{1,4} and Sylvia Cohen-Kaminsky¹

¹Univ Paris-Sud, Université Paris-Saclay, Inserm UMR-S999, Le Plessis Robinson, France

²Groupe de Recherche en Hypertension Artérielle Pulmonaire, CRIUCPQ, Quebec, Canada

³UR1197, Unité de Neurobiologie de l'Olfaction (NBO), Jouy-en-Josas, France

⁴AP-HP, Hôpital Bicêtre, Le Kremlin Bicêtre, France

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Abstract

Pulmonary arterial hypertension (PAH) is a rare progressive disease due to distal vascular remodeling, leading to right heart failure and death. PSGR is an olfactory receptor (OR) that has been recently detected in peripheral tissues. Moreover, PSGR overexpression is associated with pro-proliferative phenotype in prostate cancer. Since PAH vascular cells are characterized by cancer-like over-proliferation, we hypothesized that PSGR might participate in the vascular remodeling leading to PAH.

Here we aimed to determine whether upregulation of PSGR is implicated in PAH pathological phenotype, and to explore PSGR as a novel therapeutic target in PAH.

PSGR gene and protein expressions were assessed in total lung, distal pulmonary arteries and Pulmonary Artery Smooth Muscle Cells (PASMC) and Endothelial Cells from PAH patients and controls using qRT-PCR and western blot. We evaluated proliferation and apoptosis using Ki67 and TMRM. siRNA-directed silencing of PSGR and STAT3, was used to inhibit the specific expression in PASMCs, whereas PP2 was used to inhibit Src activation.

We demonstrate that PSGR expression is significantly increased in PASMCs and isolated pulmonary arteries of PAH patients. We also show a trend to decreased Src activation and restored BMPR2 expression as a function of PSGR inhibition in PAH-PASMC. Moreover, inhibition of STAT3 and/or Src partially decreased PSGR mRNA expression. PSGR silencing reversed the PAH pro-proliferative phenotype in human PASMC.

To conclude, overexpression of PSGR leads to a pro-proliferative phenotype of PASMCs in PAH, which could be decreased by PSGR inhibition. Src-STAT3 pathway activation is potentially the bridge linking PSGR and the pathophysiology.