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

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PSGR OLFACTORY RECEPTOR: A NEW POTENTIAL TARGET IN PULMONARY ARTERIAL HYPERTENSION

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[1] *1 Univ Paris-Sud, Faculté de Médecine, Université Paris-Saclay, Le Kremlin Bicêtre, France; 2 AP-HP, Service de Pneumologie, Hôpital Bicêtre, Le Kremlin Bicêtre, France; 3 Inserm UMR_S 999, LabEx LERMIT, DHU TORINO, Hôpital Marie Lannelongue, Le Plessis Robinson, France. 4 Groupe de recherche en hypertension artérielle pulmonaire, CRIUCPQ, Québec, Canada 5 UR1197, Unité de Neurobiologie de l'Olfaction (NBO), INRA, Jouy-en-Josas, France*

Abstract:

Pulmonary arterial hypertension (PAH) is a rare progressive disease in which 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-proliferation phenotype in prostate cancer. Since PAH vascular cells are characterized by cancer-like over-proliferation, ***we hypothesize that PSGR might participate in the vascular remodeling leading to PAH.***

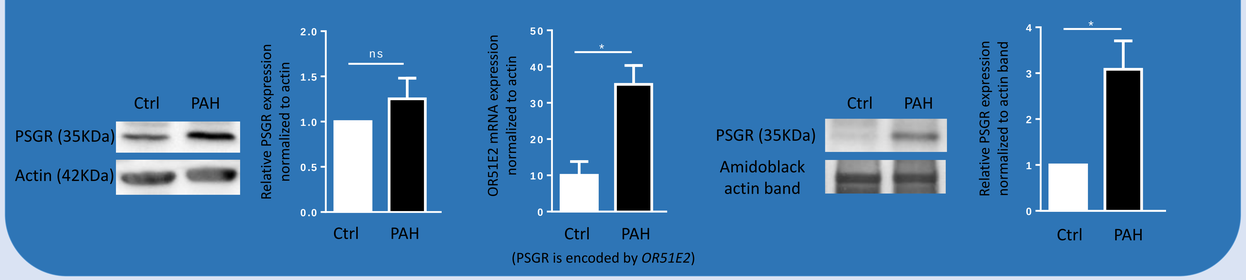
We aim to determine whether upregulation of PSGR is implicated in PAH pathological phenotype, and to explore it as a novel therapeutic target in PAH.

PSGR gene and protein expressions were assessed in total lung, distal pulmonary arteries and Pulmonary Artery Smooth Muscle (PASMC) and Endothelial Cells from PAH patients and controls using qRT-PCR and western blot. We evaluated proliferation by Ki67 and apoptosis by 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.

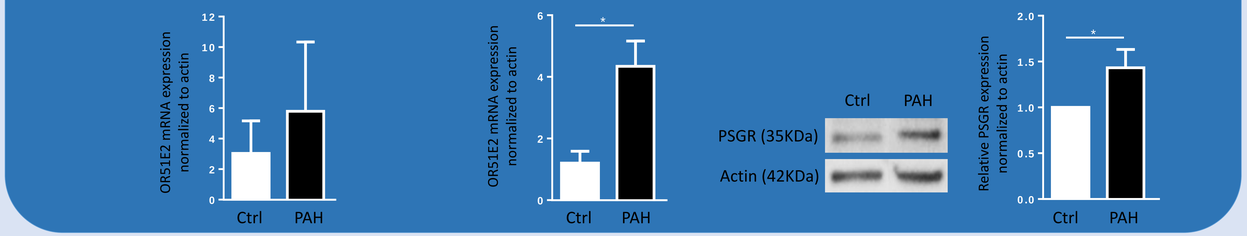
We demonstrate that PSGR expression is significantly increased in PASMC and isolated pulmonary arteries of PAH patients. We also show a trend of decreased Src activation and restored BMPR2 expression as a function of PSGR inhibition in PAH-PASMC. Moreover, inhibition of STAT3 and/or Src partially decreased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

To conclude, overexpression of PSGR leads to pro-proliferation phenotype of PASMCs in PAH, which could be decrease by PSGR inhibition. Src-STAT3 pathway activation is potentially the link between PSGR and the pathophysiology.

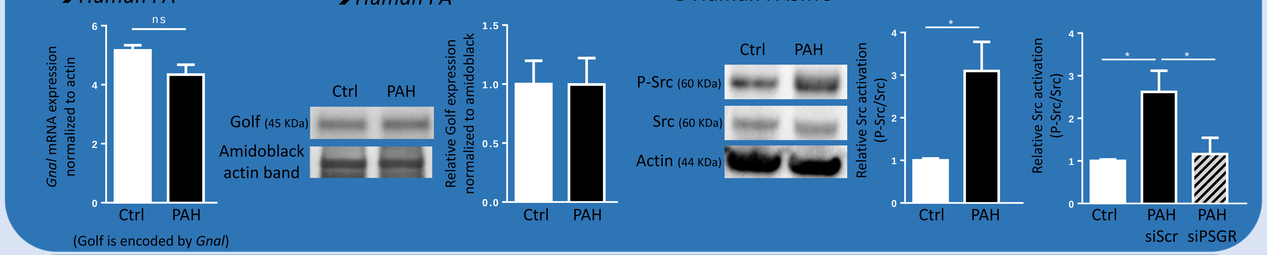
1 In human, PSGR is increased in total human lungs and in isolated Pulmonary Arteries (PA)



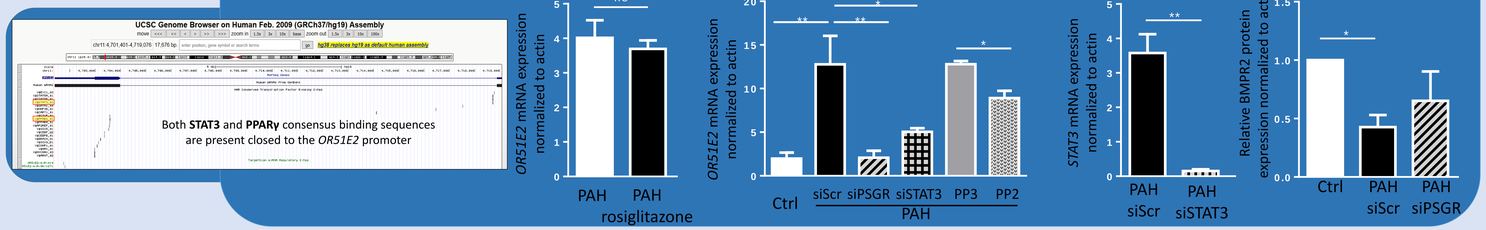
2 PSGR is significantly increased in human PAH-PASMC but not in Pulmonary Artery Endothelial Cells



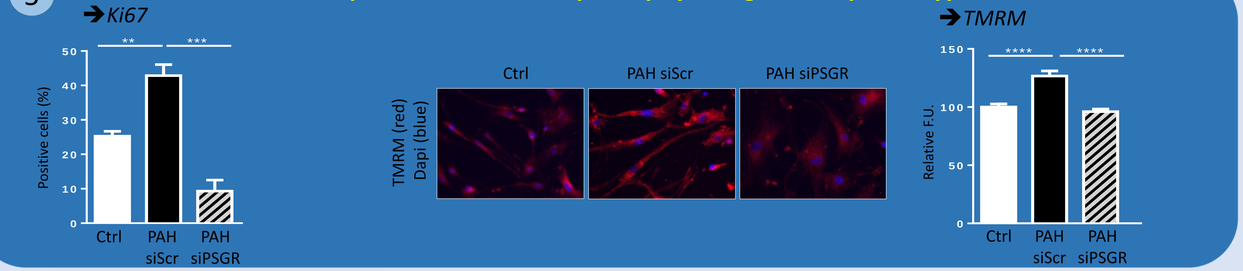
3 PSGR regulates Src activation in human PAH-pulmonary arteries

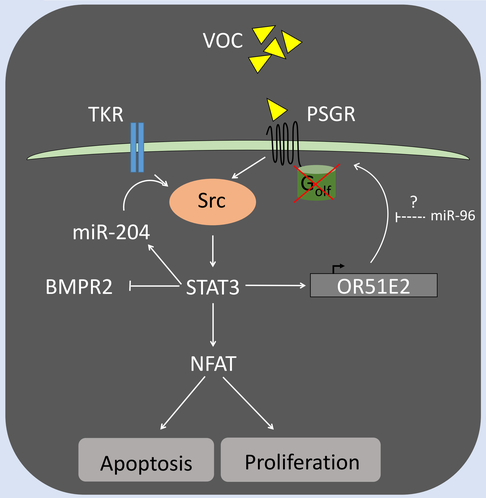


4 PSGR expression could be regulated by Src/STAT3 axis in human PAH-PASMC



5 PSGR is implicated in the PAH pathophysiological cell phenotype





Conclusion and perspectives

➔PSGR expression is increased in PAH-PASMC and in isolated human pulmonary arteries

➔PSGR is implicated in proliferation and mitochondrial membrane potential hyperpolarization.

➔PSGR siRNA-mediated downregulation decreases Src activation and restores BMPR2 protein expression in PAH-PASMC. Thus, PSGR could be implicated in PAH pathological phenotype through the Src/STAT3 axis.

➔Interestingly, PSGR mRNA expression (*OR51E2*) is partially regulated by STAT3. miR-96 involvement in OR51E2 regulation is under consideration.

➔*In vivo* experiments are ongoing to evaluate PSGR implication in experimental PH using monocrotaline rats.