Phospholipase A2 receptor 1 promotes lung cell senescence and emphysema in obstructive lung disease

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Shareable abstract (@ERSpublications)
PLA2R1 is a potent regulator of lung cell senescence in COPD, with JAK/STAT signalling as a major effector. Inhibition of JAK1/2 attenuates PLA2R1-induced lung alterations in murine models and so may represent a promising therapeutic approach for COPD. http://bit.ly/3i7yT3H

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Abstract

Background Cell senescence is a key process in age-associated dysfunction and diseases, notably chronic obstructive pulmonary disease (COPD). We previously identified phospholipase A2 receptor 1 (PLA2R1) as a positive regulator of cell senescence acting *via* Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signalling. Its role in pathology, however, remains unknown. Here, we assessed PLA2R1-induced senescence in COPD and lung emphysema pathogenesis.

Methods We assessed cell senescence in lungs and cultured lung cells from patients with COPD and controls subjected to *PLA2R1* knockdown, *PLA2R1* gene transduction and treatment with the JAK1/2 inhibitor ruxolitinib. To assess whether *PLA2R1* upregulation caused lung lesions, we developed transgenic mice overexpressing *PLA2R1* (*PLA2R1*-TG) and intratracheally injected wild-type mice with a lentiviral vector carrying the *Pla2r1* gene (LV-*PLA2R1* mice).

Results We found that *PLA2R1* was overexpressed in various cell types exhibiting senescence characteristics in COPD lungs. *PLA2R1* knockdown extended the population doubling capacity of these cells and inhibited their pro-inflammatory senescence-associated secretory phenotype (SASP). PLA2R1-mediated cell senescence in COPD was largely reversed by treatment with the potent JAK1/2 inhibitor ruxolitinib. Five-month-old *PLA2R1*-TG mice exhibited lung cell senescence, and developed lung emphysema and lung fibrosis together with pulmonary hypertension. Treatment with ruxolitinib induced reversal of lung emphysema and fibrosis. LV-*PLA2R1*-treated mice developed lung emphysema within 4 weeks and this was markedly attenuated by concomitant ruxolitinib treatment.

Conclusions Our data support a major role for PLA2R1 activation in driving lung cell senescence and lung alterations in COPD. Targeting JAK1/2 may represent a promising therapeutic approach for COPD.