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Myeloid-cell-specific deletion of inducible nitric oxide synthase protects against smoke-induced pulmonary hypertension in mice

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Shareable abstract (@ERSpublications)
Deletion of iNOS in myeloid cells protects mice against smoke-induced PH. Cross-talk of M2 macrophages with PASMCs drives smoke-induced pulmonary vascular remodelling and depends on iNOS expression in macrophages and ERK activity in PASMCs. https://bit.ly/3itDtuV

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Abstract

Background Pulmonary hypertension (PH) is a common complication of COPD, associated with increased mortality and morbidity. Intriguingly, pulmonary vascular alterations have been suggested to drive emphysema development. Previously, we identified inducible nitric oxide synthase (iNOS) as an essential enzyme for development and reversal of smoke-induced PH and emphysema, and showed that iNOS expression in bone-marrow-derived cells drives pulmonary vascular remodelling, but not parenchymal destruction. In this study, we aimed to identify the iNOS-expressing cell type driving smoke-induced PH and to decipher pro-proliferative pathways involved.

Methods To address this question we used 1) myeloid-cell-specific iNOS knockout mice in chronic smoke exposure and 2) co-cultures of macrophages and pulmonary artery smooth muscle cells (PASMCs) to decipher underlying signalling pathways.

Results Myeloid-cell-specific iNOS knockout prevented smoke-induced PH but not emphysema in mice. Moreover, iNOS deletion in myeloid cells ameliorated the increase in expression of CD206, a marker of M2 polarisation, on interstitial macrophages. Importantly, the observed effects on lung macrophages were hypoxia-independent, as these mice developed hypoxia-induced PH. *In vitro*, smoke-induced PASMC proliferation in co-cultures with M2-polarised macrophages could be abolished by iNOS deletion in phagocytic cells, as well as by extracellular signal-regulated kinase inhibition in PASMCs. Crucially, CD206-positive and iNOS-positive macrophages accumulated in proximity of remodelled vessels in the lungs of COPD patients, as shown by immunohistochemistry.

Conclusion In summary, our results demonstrate that iNOS deletion in myeloid cells confers protection against PH in smoke-exposed mice and provide evidence for an iNOS-dependent communication between M2-like macrophages and PASMCs in underlying pulmonary vascular remodelling.

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