Diverse roles of nitric oxide synthases in the pathogenesis of lung diseases

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To a greater or lesser extent, all three isoforms of nitric oxide synthases (nNOS, iNOS, and eNOS) are expressed in the lung under both physiological and pathological conditions. Although the role of NOSs in lung diseases has been examined in pharmacological studies with non-selective NOSs inhibitors, it still remains to be fully elucidated due to non-specificity of the agents. We addressed this point in our mice lacking all three NOSs and in mouse lung disease models. Bleomycin treatment significantly increased pulmonary fibrosis, collagen content in the lung, and the total cell number in bronchoalveolar lavage fluid in wild-type (WT), single $nNOS^{-/-}$, $iNOS^{-/-}$, and $eNOS^{-/-}$, and triple $n/i/eNOSs^{-/-}$ mice as compared with saline treatment. Those changes were significantly exacerbated only in the triple $NOSs^{-/-}$ mice, but not in any single $NOS^{-/-}$ mice, as compared with the WT mice, suggesting a protective role of NOSs in the development of pulmonary fibrosis (*Respir Res* 2014). Chronic hypoxic exposure significantly caused an increase in right ventricular pressure, right ventricular hypertrophy, and pulmonary artery remodeling in all the WT, single $NOS^{-/-}$, and triple $NOSs^{-/-}$ mice as compared with normoxic exposure. Those alterations were significantly aggravated in the triple $NOSs^{-/-}$ mice and, to a lesser extent, in the $eNOS^{-/-}$ mice as compared with the WT mice, again suggesting a protective role of NOSs in the development of pulmonary hypertension (*AJRCCM* 2018). In contrast, ovalbumin-induced bronchial thickening, eosinophilic infiltration, and mucus secretion were markedly mitigated in the triple $NOSs^{-/-}$ than in the WT mice, suggesting an opposing injurious role of NOSs in the development of bronchial asthma (*Lung* 2016). These results suggest that, even in the same lung organ, the role of NOSs appears to be different in distinct disease conditions, demonstrating diverse roles of NOSs in the pathogenesis of lung disorders.