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International Conference on

HEART CONGRESS, VASCULAR BIOLOGY AND SURGEON'S MEETING

December 04-05, 2017 Dallas, USA

Ascorbate prevents cigarette smoke-induced lung alveolar damage and vascular remodeling

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Cigarette smoke (CS) not only causes emphysema, a fatal disease involving progressive destruction of the lung alveoli but also induces right ventricular dysfunction due to pulmonary hypertension in chronic smokers. Here we show that guinea pigs exposed to sustained CS exposure over 10 weeks, undergo extensive emphysematous alveolar damage accompanied by pulmonary vascular remodeling that is implicated to the pulmonary hypertension. While the observed alveolar damage is characterized by an enlargement of pulmonary air spaces due to proteolytic degradation of the extracellular matrix proteins constituting the alveolar wall and extensive cellular apoptosis, the pulmonary vessel remodeling shows increased adventitia, peri-vascular fibrosis and thickening of the vessel wall. We demonstrate that such diverse pathological fates of the lung tissue are not only triggered by CS-induced oxidative stress but are also mobilized through distinct immunological pathways defined by diverse cytokine involvement. Besides directly oxidizing lung proteins, tobacco smoke induces release of the cytokines TNFα and IL-8 along with the pro-inflammatory factor, Rtp801 which in turn causes overproduction of nitric-oxide (NO) by inducible NOS (iNOS) as well as superoxide, which combine to produce, peroxynitrite, a potent oxido-nitrosative species that contributes to extensive lung protein nitration. Such nitrated lung proteins along with those oxidized directly by tobacco smoke oxidants become susceptible to proteolysis by lung proteases causing extensive destruction of the lung alveoli. Lung-specific administration of an anti-inflammatory glucocorticoid to the CS-exposed guinea pigs revealed that tobacco smoke oxidants and not the oxido-nitrosative species generated in the lung are predominantly responsible for the observed cigarette smoke-induced lung alveolar damage marked by the increased expression of TNFα and IL8. However, sustained tobacco smoke exposure was found to induce the release of increased levels of TGF-β, the major pro-fibrotic cytokine, which predisposed the lung vasculature to remodelling. Such different cytokine(s) involvement is also responsible for mobilizing diverse enzymatic pathways, which results in the concurrent occurrence of two contrasting pathological events within the lung tissue during smoking - alveolar destruction and vascular remodeling. Interestingly inhibition of the inflammatory enzyme inducible nitric oxide synthase (iNOS) by an iNOS-specifc inhibitor, L-NIL despite preventing protein nitration, could not forestall CS induced protein oxidation or alveolar damage. Our results indicate that iNOS inhibition actually enhanced CS induced vascular remodeling. The dietary antioxidant ascorbate on the other hand, substantially prevented both alveolar destruction as well as vascular remodeling presumably by inhibiting the initiating tobacco smoke and ROS induced lung protein oxidation and the consequent generation of the responsible cytokines. Taken together, our results indicate the major role of tobacco-smoke oxidant(s) as the primary etiopathogenic factor behind lung alveolar damage and as a significant contributor to pulmonary vascular remodelling witnessed during cigarette smoke-induced lung damage along with the endogenous oxidants generated by inflammation. Our results also highlight the versatile capability of the inexpensive antioxidant, vitamin C in the prevention of both forms of damage through the abrogation of the causal tobacco smoke induced oxidative damage.

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