Reduced Supply of Monocyte-derived Macrophages Leads to a Transition from Nodular to Diffuse Lesions and Tissue Cell Activation in Silica-induced Pulmonary Fibrosis in Mice

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Progressive pulmonary fibrosis (PF) has a poor-prognosis with limitation of its treatment. Various types of lung macrophages, including alveolar macrophages, interstitial macrophages, and monocyte-derived macrophages (MMs) have been implicated in the progression and resolution of bleomycin-induced diffuse PF. However, it remains unclear how macrophages contribute to silica-induced progressive nodular PF and the associated tissue cell responses *in vivo*. To address these questions, we treated *Col1a2*-GFP reporter mouse lung with a single-dose of bleomycin or silica to induce reversible or progressive PF, respectively, and compared the kinetics of macrophage subsets and lung tissue cells between models with flow-cytometry based quantification. Here, we show that lack of MMs results in the formation of diffuse PF after silica instillation. We found that the proportion and the number of MMs and interstitial macrophages were persistently higher in silica-induced progressive PF as compared to bleomycin-induced PF. In contrast, the number of alveolar macrophages was persistent both in silica- and bleomycin-induced PF. Surprisingly, in *Ccr2*$^{-/-}$ mice, in which MM infiltration is impaired, silica administration induced diffuse PF with loose nodule formation and greater activation of tissue cells. In the diffuse lesions, the distribution of epithelial cells, distribution of myofibroblasts and architecture of the basement membrane were disrupted. Consistent with the development of diffuse lesions, genes that were differentially expressed in CD45^{-} tissue cells from the lung of WT and *Ccr2*$^{-/-}$ mice were highly enriched in human diffuse-progressive PF. In gene ontology network analyses, many of these genes were associated with tissue remodeling, and included genes not previously associated with PF, such as Mmp14, Thbs2, and Fgfr4. Overall, these results demonstrate that MMs prevent transition from nodular to diffuse silica-induced PF, potentially by regulating tissue cell responses.

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CoO and La2O3 nanoparticle-induced pulmonary response in mice after whole-body inhalation exposure

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Metal oxide nanoparticles have the unique property of semi-conduction and can serve as conduits for electron transfer between aqueous reactants. Studies have shown that these semi-conducting properties may be responsible for generating adverse health effects. Two metal oxide nanoparticles with different semi-conductor properties, cobalt monoxoide (CoO) and lanthanum oxide (La_2O_3) may pose different toxicological potentials *in vivo* and *in vitro*. Our previous *in vitro* study showed that CoO nanoparticles induce a more potent toxicological response in human small airway epithelial cells than La_2O_3 nanoparticles. The current study determined CoO and La_2O_3 metal oxide nanoparticles-induced pulmonary response in mice after whole-body inhalation exposure. Mice were exposed to 10 or 30 mg/m^3, for 6 h per day over 4 days and were examined at 1, 7 and 56 days post exposure. Both CoO and La_2O_3 nanoparticles were present in the lung at 1, 7 and 56 days post exposure; however, CoO caused greater lactate dehydrogenase, macrophages, lymphocytes, neutrophils and eosinophils in the bronchoalveolar fluid compared to La_2O_3 nanoparticles at both doses and all post exposure time points. Histopathological results show that there was acute pulmonary inflammation at 1 day post-exposure for both nanoparticles; however, no chronic fibrotic response was observed. Mice exposed to CoO had higher levels of proinflammatory cytokine expression compared to mice exposed to La_2O_3 nanoparticles. Taken together, the results demonstrate that CoO nanoparticles induce more overall acute pulmonary toxicity when compared to La_2O_3 nanoparticles. Moreover, this study starts to fills the gap between *in vivo* and *in vitro* nanoparticle-induced toxicity studies and risk assessment.

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POSTER NUMBER: 1003

The Matricellular Protein Periostin (POSTN) is a Potent Stimulus for Lysyl Oxidase I in Hepatic Fibrosis

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POSTN, a secreted 90kDa matricellular glycoprotein, is involved in embryologic development as well as in the pathogenesis of metastatic tumor development and organ fibrosis. A recent manuscript demonstrated POSTN global null (KO) mice failed to develop significant liver fibrosis following carbon tetrachloride (CCl_4) gavage. Here we provide a mechanistic explanation as to how POSTN functions as a non-structural regulatory protein in the genesis and maintenance of the hepatic extracellular matrix (ECM).

In vitro studies were conducted with primary cultured rat hepatic stellate cells (HSCs) exposed to 100 ng/ml POSTN. POSTN activated focal adhesion kinase (FAK) as assessed by phosphorylation of tyr576/577 and tyr925 by Western blot. Downstream POSTN resulted in Akt phosphorylation and nuclear translocation of p65 (NFkappaB). In the presence of POSTN, blocking antibodies against either aphaVbeta3 or alpha5 integrins abolished all these signaling events. Also, siFAK blocked POSTN mediated Akt phosphorylation and NFkappaB translocation. We also demonstrated POSTN binds HSC discoidin domain receptor I (DDR1) by immunoprecipitation of POSTN from activated HSC lysates, and immunoblot with anti-DDR1 antibodies.

In vivo, livers of POSTN global KO mice, following 5 weeks of CCl_4 gavage, revealed a marked absence of dense collagen fibrils compared to WT mice as seen by transmission electron microscopy; and, Sirius Red density was diminished as visualized with light microscopy. Atomic-force microscopy also demonstrated decreased liver stiffness in POSTN KO mouse livers compared to WT mice. Whole liver lysates subjected to western blot, revealed reduced lysyl oxidase I expression from POSTN KO mice as compare to WT mice

POSTN is a major player in maintenance of ECM molecular integrity and stiffness in liver fibrosis.

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Unfolded Protein Response and Endoplasmic Reticulum Localized Oxidoreductase-ERp57 Regulates Allergic Lung Inflammation and Fibrosis

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Evidence for association between asthma and the unfolded protein response (UPR) is emerging. ERp57 is an ER localized oxidoreductase involved in folding and secretion of glycoproteins. We have previously demonstrated that ERp57 is up regulated in allergen-challenged human and murine lung epithelial cells. However, the role of ERp57 in asthma pathophysiology is unknown.

Here, we sought to examine the contribution of airway epithelial-specific UPR and ERp57 in the pathogenesis of allergic asthma, and the effect of allergen-induced innate and adaptive immune responses on the induction of UPR and airways fibrosis.