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Aquaporin-1 as a Differential Marker in Toxicant-Induced Lung Injury

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Abstract : Background and Significance: Respiratory exposure to toxicants (chemicals or particulates) causes disruption of lung homeostasis leading to lung toxicity/injury manifested as pulmonary inflammation, edema, and/or other effects depending on the type and extent of exposure. This emphasizes the need for investigating toxicant type-specific mechanisms to understand therapeutic targets. Aquaporins, aka water channels, are known to play a role in lung homeostasis. Particularly, the two major lung aquaporins AQP5 and AQP1 expressed in alveolar epithelial and vasculature endothelia respectively allow for movement of the fluid between the alveolar air space and the associated vasculature. In view of this, the current study is focused on understanding the regulation of lung aquaporins and other targets during inhalation exposure to toxic chemicals (Cigarette smoke chemicals) versus toxic particles (Carbon nanoparticles) or co-exposures to understand their relevance as markers of injury and intervention. Methodologies: C57BL/6 mice (5-7 weeks old) were used in this study following an approved protocol by the University of Cincinnati Institutional Animal Care and Use Committee (IACUC). The mice were exposed via oropharyngeal aspiration to multiwall carbon nanotube (MWCNT) particles suspension once (33 ugs/mouse) followed by housing for four weeks or to Cigarette smoke Extract (CSE) using a daily dose of 30µl/mouse for four weeks, or to co-exposure using the combined regime. Control groups received vehicles following the same dosing schedule. Lung toxicity/injury was assessed in terms of homeostasis changes in the lung tissue and lumen. Exposed lungs were analyzed for transcriptional expression of specific targets (AQPs, surfactant protein A, Mucin 5b) in relation to tissue homeostasis. Total RNA from lungs extracted using TRIreagent kit was analyzed using qRT-PCR based on gene-specific primers. Total protein in bronchoalveolar lavage (BAL) fluid was determined by the DC protein estimation kit (BioRad). GraphPad Prism 5.0 (La Jolla, CA, USA) was used for all analyses. Major findings: CNT exposure alone or as co-exposure with CSE increased the total protein content in the BAL fluid (lung lumen rinse), implying compromised membrane integrity and cellular infiltration in the lung alveoli. In contrast, CSE showed no significant effect. AQP1, required for water transport across membranes of endothelial cells in lungs, was significantly upregulated in CNT exposure but downregulated in CSE exposure and showed an intermediate level of expression for the co-exposure group. Both CNT and CSE exposures had significant downregulating effects on Muc5b, and SP-A expression and the co-exposure showed either no significant effect (Muc5b) or significant downregulating effect (SP-A), suggesting an increased propensity for infection in the exposed lungs. Conclusions: The current study based on the lung toxicity mouse model showed that both toxicant types, particles (CNT) versus chemicals (CSE), cause similar downregulation of lung innate defense targets (SP-A, Muc5b) and mostly a summative effect when presented as co-exposure. However, the two toxicant types show differential induction of aquaporin-1 coinciding with the corresponding differential damage to alveolar integrity (vascular permeability). Interestingly, this implies the potential of AQP1 as a differential marker of toxicant type-specific lung injury.

Keywords : aquaporin, gene expression, lung injury, toxicant exposure
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