

## Barrier function and ion transport in an oleic acid-induced model of lung injury

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Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are life threatening conditions characterized by disruption of the alveolo-capillary barrier leading to fluid accumulation in the lungs, inflammation and impaired gas exchange. Current treatments for ALI and ARDS focus on management of mechanical ventilation to prevent further damage. Recent studies have suggested the possibility of pharmacological interventions (Han and Malampalli (2015)), however the molecular mechanisms and signalling pathways underlying the functional changes in the disease need to be better understood for successful development of clinical therapies. Here we report on the characterisation of an *in vitro* lung injury model using oleic acid treatment of the alveolar epithelial-like cell line NCI-H441.

NCI-H441 cells were cultured on a permeable membrane with the apical surface exposed to air to mimic the *in vivo* alveolar epithelium. Lung injury was induced by exposing the basolateral surface of the cells to varying concentrations of oleic acid (0 – 25  $\mu$ M). Oleic acid disrupted barrier integrity and active ion transport as assessed by a drop in transepithelial electrical resistance (upto 81% of baseline), potential difference (upto 83% of baseline) and net sodium transport (upto 90% of baseline). The nature of the barrier damage was further investigated by measuring the apparent permeability to paracellular polyethylene glycol (PEG) tracers (molecular mass 239 – 1200 Da) and fitting a two-pore sieving model. The results indicated that oleic acid disrupts the barrier by increasing the number and/or size of the larger pores in the epithelium. The functional responses were accompanied by alterations in the expression of tight junction proteins claudin-3 (reduced by 50%) and zona occludens-1 (increased by 200%), sodium-potassium ATPase (reduced by 60%) and the beta subunit of the epithelial sodium channel ( $\beta$ -ENaC, reduced by 40%). The results quantify the functional changes in an oleic acid-induced lung injury model and identify the proteins involved in the response. This lays the foundation for identifying and possibly manipulating the regulatory pathways to treat ALI/ARDS.

Han S & Malampalli RK. (2015) The acute respiratory distress syndrome: from mechanism to translation. *J Immunol* **194**(3): 855-860.