ZINC DEFICIENCY ENHANCES DEATH RECEPTOR-MEDIATED APOPTOSIS IN DIFFERENTIATED PRIMARY HUMAN LUNG EPITHELIAL CELLS

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Introduction: Intracellular zinc deficiency has been identified as a predisposing factor to lung epithelial damage in diseases such as asthma and ARDS. In this investigation we determined if intracellular zinc deficiency makes the lung epithelium more susceptible to death receptor-mediated apoptosis and barrier dysfunction.
Hypothesis: Zinc deficiency will enhance death receptor activation of the lung epithelium resulting in enhanced cellular apoptosis and breakdown of barrier function.
Methods: An in vitro model of fully differentiated primary human airway epithelia was established to monitor cellular function and barrier integrity. Cultures from multiple donors were exposed at the apical or basolateral surface to a combination of biologically relevant factors associated with acute lung injury (IFNg 250 U/ml, TNFa 100 ng/ml, and a Fas cross-linking antibody (FasAb) 200 ng/ml). Transepithelial resistance (Rt) was measured across culture inserts with a portable ohmmeter. Caspase-8 and –3 enzymatic activity was recorded while cellular apoptosis was detected immunohistochemically by cytoplasmic localization of caspase cleaved cytokeratin-18. Barrier function and paracellular transport were measured by Lucifer Yellow flux.
Results: Exposure to IFNg, TNFa and FasAb at the basolateral surface resulted in a moderate increase in caspase function and apoptosis (10-20%) without evidence of barrier disruption. However, exposure to all factors in the presence of zinc deficiency resulted in an abrupt decrease in Rt, increased paracellular leak and an increase in apoptosis (50-70%). Substantially less apoptosis occurred following exposure at the apical surface which was explained by polarized expression of Fas receptor at the basolateral surface. Addition of Zinc sulphate to zinc deficient cells prevented apoptosis and loss of barrier function.
Conclusions: From our findings we conclude that subacute zinc deficiency may predispose patients to increased lung injury in diseases associated with inflammation and death receptor activation.

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