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Title: Impact of influenza virus infection on alveolar epithelial cell Na,K-ATPase expression and localization

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Body: Influenza A viruses (IV) cause primary viral pneumonia resulting in acute lung injury (ALI) associated with a decreased alveolar fluid clearance (AFC), which under normal conditions is driven by the basolateral Na,K-ATPase. Therefore we investigate the regulation of Na,K-ATPase in IV-infection by viral and host factors to characterize the mechanisms affecting AFC. The effects of IV-infection on Na,K-ATPase have been studied in primary murine and human alveolar epithelial cells (AEC) in monoculture and in coculture with macrophages. Cells were infected with A/PR/8/1934 (PR8) and Na,K-ATPase expression and localization was analysed by qPCR, Western blot, flow cytometry and confocal microscopy. Na,K-ATPase was not regulated on mRNA levels upon IV-infection in mAEC. Protein levels of Na,K-ATPase α1 were significantly decreased in total cell lysates and surface fractions during IV-infection. Interestingly, Na,K-ATPase α1 surface expression was primarily decreased in non-infected cells, whereas IV-infected cells showed little reduction in Na,K-ATPase α1 expression. Cocultivation of AEC with infected macrophages enhanced the degradation of Na,K-ATPase α1 protein levels, likely by a soluble mediator. Of note, confocal microscopy revealed a mistargeting of Na,K-ATPase α1 to the apical membrane in infected AEC, lungs of infected mice and after transfection of the viral M segment. We provide evidence that AFC in IV-infection is impaired by viral and host factors affecting Na,K-ATPase expression levels and localization. Defining the underlying molecular pathways might provide targets for new treatments increasing edema clearance in IV-induced ALI.