Title: Role of Dual Oxidase 1 in influenza A infection

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During influenza infection, the broncho-epithelial cells orchestrate an oxidative extracellular antiviral system in the airway surface liquid. This system is composed of the protein lactoperoxidase (LPO), the thiocyanate ion (SCN-), and hydrogen peroxide (H_2O_2) generated by Dual oxidase 1 (DUOX1), a member of the Nicotinamide Adenine Diphosphate Hydrogenase family. LPO oxidizes SCN- using H_2O_2 into virucidal hypothiocyanite (OSCN-). This system has *in vitro* virucidal effects but its occurrence *in vivo* during influenza A infection is largely unknown. DUOX1, highly expressed in apical membrane of broncho-epithelial cells, is the source of hydrogen peroxide in the LPO/H_2O_2/SCN system. We hypothesize that DUOX1 is a major player in the innate immune response against influenza A infection *in vivo*. Using a mouse model of influenza A infection with Duox1-deficient and C57BL/6 mice, we investigated whether Duox1 attenuates influenza A virus infection, primarily by inducing extracellular virion inactivation and coordinating the early innate immune response to infection *in vivo*. Mice, both Duox1-deficient and C57BL/6 mice are infected with PR8 mouse-adapted influenza A virus strain. A group of mice was followed-up overtime for survival and weight loss and another group was serially sacrificed. In some mice, the broncho-alveolar lavage was collected for protein isolation and multicolor flow cytometry staining on isolated cells in suspension. Lung and trachea were collected in other mice and fixed in formalin for histopathology and immunostaining. Duox1 and Duox2 protein expression in both Duox1-deficient and wild type mice were assessed by immunohistochemistry and immunofluorescence staining in both lung and trachea. Viral load is estimated by immunohistochemistry and luminex assay is used to measure panels of chemokines and cytokines from the broncho-alveolar lavage. Our data have shown so far, that Duox1-deficient mice are more susceptible to influenza A challenge and susceptibility is associated with an increased inflammatory response composed of monocytes/macrophages and neutrophils. Duox1 protein expression is higher in both lung and trachea tissues of IAV-infected C57BL/6 mice relative to Duox1-deficient mice.

These results indicate that Duox1 has a critical role in innate immune defense against IAV.