Influenza A-Induced Lung Injury And Mortality Is Increased In Obese Mice Through A Leptin Independent Mechanism

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Rationale: Obesity was associated with increased rates of mortality during the recent H1N1 outbreak. We used a murine model of influenza A pneumonia and acute lung injury to test the hypothesis that leptin resistance, a feature of the metabolic syndrome, might explain the enhanced mortality in obese patients.

Methods: For our experiments, we used C57Bl/6 (wild-type), db/db mice (mice with global leptin resistance due to defective leptin receptor) and generated SP-C-Cre$^{+/+}$/LepR$^{fl/fl}$ (mice with leptin resistance specifically within lung epithelium) and LysM-Cre$^{+/+}$/LepR$^{fl/fl}$ mice (mice with leptin resistance specifically within macrophages and neutrophils). In contrast to db/db mice, SP-C-Cre$^{+/+}$/LepR$^{fl/fl}$ and LysM-Cre$^{+/+}$/LepR$^{fl/fl}$ mice are non-obese. We intratracheally intubated and infected the mice with A/WSN/33 [H1N1] influenza A virus (500 and 1500 pfu/mouse). After influenza infection, leptin levels, cell count and differential, protein and cytokines were measured in the bronchoalveolar lavage (BAL) fluid. Lung homogenates were also obtained for measurement of viral load using plaque assays along with histologic evaluation. After influenza infection, wild type mice were also treated with either PBS or leptin 0.5 mg/kg S.C. twice daily with subsequent measurement of daily weight and mortality.

Results: Influenza A infection increased levels of leptin in BAL fluid in wild-type mice. The severity of lung inflammation (BAL fluid cell count and proinflammatory cytokine levels) and lung injury (BAL fluid total protein, lung histology and mortality) was significantly worse in the db/db compared to wild-type mice. In contrast, non-obese, SP-C-Cre$^{+/+}$/LepR$^{fl/fl}$ and LysM-Cre$^{+/+}$/LepR$^{fl/fl}$ had prolonged survival following influenza A infection. Examination of viral clearance using plaque assays revealed impaired viral clearance in the db/db mice and improved viral clearance in the SP-C-Cre$^{+/+}$/LepR$^{fl/fl}$ mice and LysM-Cre$^{+/+}$/LepR$^{fl/fl}$. Consistent with these results, exogenous administration of leptin resulted in earlier mortality in wild-type mice after influenza A infection.

Conclusions: Globally leptin resistant, obese mice demonstrated worsened lung injury and impaired viral clearance during influenza A pneumonia, mirroring clinical observations seen in obese humans. However, the loss of leptin signaling in the lung epithelium or macrophages attenuated influenza A-induced mortality. These results suggest that leptin signaling in lung epithelium or macrophages is not responsible for the worsened outcomes in obese humans during influenza A infection.

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