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High concentrations of PGE2 in diet-induced obese mice bestows the impaired innate immune responses to H1N1 influenza virus infection

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To better understand how obesity leads to increased susceptibility to virus infections and to develop effective treatments, we used a diet-induced obese mouse model to demonstrate the well-recognized chronic systemic inflammatory status associated with obesity were heavily affecting the innate defense in respiratory system. A significant rise in inflammatory cytokines (IL1, IL-6 and TNFα□□and chemokines (MCP-1, MIP1, and RANTES etc.) was detected by bead-based multiplex immunoassay in lung tissue homogenates of obese mice comparing to regular weight lean mice. Concurrently, obese mice had dramatically higher concentration of lipid inflammatory mediator, prostaglandin E2, in the lung and serum. Cyclooxygenase 2 (COX2) and other genes participated in PGE2 biosynthesis were significantly upregulated in obese mouse lung tissues as well. PGE2 has been shown to modulate immune and inflammatory responses. However, the augmented pulmonary inflammatory mediators were found to have negative impact or immune suppressive effects against influenza infection in our animal model. When those obese mice were challenged intranasally with 2009 pandemic H1N1 virus, they only mounted a blunted innate response showing a delayed cytokine gene induction and less inflammatory cell infiltrations at the site of infection at day 1 and day 3 postinfection (p.i.) while the lean mice showed quick and higher level of pro-inflammatory cytokines, type I interferon's and anti-inflammatory cytokine IL10 induction. Our in vitro study also demonstrated that a suppressed cytokine responses to LPS stimulation in obese mouse alveolar macrophage (AM) than that of lean mice AM; furthermore, we demonstrated that the immune suppression substances in obese mouse lung homogenates could be attributed to PGE2. To further support this finding, we treated obese mice with paracetamol (100 mg/kg) for three days before virus challenge and found that the expression of cytokine genes was significantly enhanced comparing to those untreated mice at day 1, 3, post infection. Paracetamol treatment alone started three days before infection until six days after infection also ameliorated the severity of the disease in H1N1 infected obese mice showing lesser body weight loss, less lung pathological changes and improved survival. In conclusion, our data indicate that the pre-existing high levels of pulmonary PGE2 plays a significant role to suppress the innate response of obese mice to influenza infection, and modulating PGE2 production, by paracetamol, can help to lessen the impact by influenza viral infection.

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