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HDACs INHIBITOR TRICHOSTATIN A ENHANCES DISEASE SEVERITY AND LUNG PATHOLOGY IN INFLUENZA A/H3N2-INFECTED MICE

Content

Histone deacetylases (HDACs) are epigenetic factors modulating gene expression related to numerous biological processes including inflammation. All mechanisms can turn on/off the transcription of genes creating a network of reinforcing or counteracting signals in the cell. Thus, the application of molecules - inhibitors/activators that alter their activity might influence in an unexpected manner pathological condition such as the influenza infection.

Herein, as a pilot study, we selected Trichostatin A (TSA) as a standard substance known to inhibit HDACs to test primarily our hypothesis that it might affect pathology in influenza-infected mice. TSA was administered subcutaneously at a dose of 10 mg/kg/day to ICR mice in a 5 day-lasting course. We followed-up the survival, as well as lung viral titers, macroscopic pulmonary changes and histology on the 5th day p.i. A group treated with the optimal dose of 10 mg/kg/day reference compound oseltamivir phosphate served to compare the antiviral responses in vivo.

We found that TSA failed to exert protective effect in experimental influenza A H3N2- infected mice. The survival of TSA-treated and infected animals was lower than in the placebo control. Indeed, TSA administration increased lung score indicative for severe exudate formation 2 times more as compared to the reference antiviral. Lung viral titer in TSA-treated mice with flu exceeded that in the untreated infected mice by 0.67 Lg. Correspondingly we observed alterations in the lung histology showing increased inflammation, fibrosis and respiratory distress syndrome. In the control group the dose of 10 mg/kg oseltamivir phosphate lead to 80% mice survival, decreased lung pathology and virus titer.

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