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Trichostatin A Attenuates Airway Inflammation in Mouse Asthma Model

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Introduction

Histone deacetylase (HDAC) inhibition has been demonstrated to change the expressions of a restricted set of cellular genes. T cells have an essential role in the pathogenesis of allergen-induced airway inflammation [1]. In recent studies, it has been demonstrated that treatment with HDAC inhibitors induces a T cell-suppressive effect [2]. The purpose of this study was to determine whether treatment with trichostatin A (TSA), a representative HDAC inhibitor, would reduce the allergen-induced airway inflammation in a mouse asthma model.

Materials and Methods

BALB/c mice were sensitized to ovalbumin (OVA), by intraperitoneal (i.p.) injection, and challenged with an aerosol of OVA. TSA was injected intraperitoneally every two days beginning on day, at a dose of 1mg/kg of body weight. The immunohistochemistry (IHC) for the HDAC1, one of major HDAC subtypes, in normal and asthmatic lungs of the mice were performed. The mice were analyzed for the effect of TSA on the airway hyperresponsiveness (AHR), inflammatory cell number, and cytokine and IgE levels in the bronchoalveolar lavage (BAL) fluid. The infiltration of CD4+ cells was also analyzed using IHC.

Results

The HDAC1 was localized within the in most cells of airway, and infiltrated the inflammatory cells of the asthmatic lungs like previous report [3]. Treatment with TSA significantly attenuated the AHR. The numbers of eosinophil and lymphocyte in the BAL fluid were reduced by treatment with TSA. Infiltration of the inflammatory cells and mucus occlusions in lung tissue, were also significantly weakened by treatment with TSA. The levels of IL-4, IL-5, and IgE in BAL fluid were markedly decreased by treatment with TSA. In addition, the TSA treated mice also showed reduced infiltration of the CD^{4+} cells in the lungs.

Discussion

In this study, it has been demonstrated that the HDAC inhibition by treatment with TSA attenuated allergen-induced airway inflammation in a mouse asthma model. Recently, FR901228 and TSA, specific HDAC inhibitors, have been reported as having immunosuppressive effects by reducing proliferation, IL-2 production and CD154 of CD^{4+} T cells. Furthermore, HDAC inhibitionby TSA or SAHA also reduces the renal disease in a murine model of lupus by downregulating the production of both Th1 and Th2 cytokines. Thus, HDAC inhibitors may inhibit effectively the activity of T cells in vivo. In this study, TSA reduced the number of lymphocytes in the BAL fluid, and the infiltration of CD^{4+} T cells in the lungs. Representative Th2 cytokines, including IL-4 and IL-5, were significantly reduced by the TSA treatment. Thus, the inhibitory effects of TSA on T cells attenuate the allergen-driven airway inflammation and AHR. From our results, histone acetylation appears to play an important role in the development of asthma, and the HDAC inhibitors may be therapy for allergic airway inflammation.

References

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