Abstract

Objective:
This study was conducted to examine whether nasal mucosa of patients with allergy might be more susceptible to rhinovirus (RV) infection. In addition, we investigated the effects of RV infection on the expression of co-stimulatory molecules and cytokines in patients with allergic rhinitis.

Methods:
Uncinate process mucosa were obtained from 39 patients with allergy and 22 without allergy from chronic rhinosinusitis patients, and infected with RV16 using an air-interface organ culture system. The expression level of programmed cell death ligand (PDL) 1, PD-L2, IFN-γ, IL-4, IL-5, and IL-10 were evaluated in infected nasal mucosa.

Results:
The RV infection rates were not significantly different between allergy and non-allergy group. In allergy group, RV infected tissues showed significantly elevated expression of PD-L1 and IL-10 compared to control. Whereas, non-allergy group increased levels of IL-4, IL-5 and IFN-γ compared to those of control tissues. In addition, the IL-4/IFN-γ ratio was increased after RV infection in non-allergy group but not in allergy group.

Conclusion:
Allergy and non-allergy subjects tend to have a similar degree of RV infection. Enhanced PD-L1 and IL-10 induced by RV infection in allergy group cannot efficiently handle the immune response to RV. Furthermore, elevated of IL-4/IFN-γ ratio in infected tissue from non-allergy group suggests that repeated rhinovirus infection may cause Th2 biased environment.

Introduction

Rhinovirus is a common viral pathogen associated with upper respiratory infection, and it induces expression of a wide range of co-stimulatory molecules, pleiotropic cytokines, growth factors, and chemokines. Viral modulation of inhibitory molecule B7 family on epithelial cells results in suppression or termination of immune responses. PD-L1 and PD-L2 belong to the B7 family and are widely expressed on cells such as activated T cells, B cells, monocytes, dendritic cells, macrophages and airway epithelial cells in order to modulate activation or inhibition. PD-1 activity is required for the termination of the late phase of allergic inflammation. It is reported that IL-4 induces PDL2 more preferentially than IFN-γ, while IFN-γ induces PDL1 more preferentially than IL-4 on macrophage, suggesting that Th1 and Th2 responses mobilize PDL1 and PDL2 differentially. Opposing roles are shown between PDL1 and PDL2, regarding the regulation of airway hyperresponsiveness (AHR) and invariant natural killer T (iNKT)-cell-mediated activation. By Feedback loop, the enhanced PDL1 expression inhibits IFN-γ by negative feedback loop and increases AHR. PD-L1 up-regulated by activated CD4 T cells binds to PD-1, and triggers IL-10 production. IL-10 is known to be the major anti-inflammatory cytokine with important function in controlling diverse immune responses such as preventing autoimmunity and allergic inflammatory responses. It down-regulates production of cytokines, expression of co-stimulating accessory molecules, and the processing and presentation of antigens. However, it stimulates Th2 cell, mast cells and B cell maturation and antibody production.

Methods and Materials

Study subjects
Uncinate process mucosa were obtained from 39 patients with allergic rhinitis and 21 patients without allergic rhinitis who underwent surgical management of CRS at the Seoul National University Hospital.

Methods and Materials

Effect of RV infection on Th2/Th1 balance in nasal mucosa (n=8~11)

The relative expression was calculated by dividing the amount of IL-4 / IFN-γ ratio after infection by the amount of IL-4 / IFN-γ ratio before infection in each individual. Data are expressed as Mean±SEM.

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Discussion

According our experiment result, the susceptibility to RV infection did not differ significantly. These results suggest that, under the same condition, allergic and non-allergic subjects have a similar degree of RV infection. A term of infection in our experiment means that RVs exist in nasal mucosa, while clinical diagnosis of cold means that patients complain specific symptoms of cold.

After RVs enter the upper respiratory epithelial cells, virus begins to replicate and spread, the anti-viral immune responses occur. Induction of the PD-L1 on epithelial cells occurred as a response to viral infection, a major trigger of inflammation. PD-L1 binds to PD-1 on monocytes and triggers IL-10 production. Enhanced PD-L1 and IL-10 have an ability to suppress the function of APC, and thereby down-regulating the function of dendritic cells. As shown in our data, PD-L1 and IL-10 were induced by RV infection in allergy group. In non-allergy group, IFN-γ was significantly elevated by RV infection but not in allergy group. Therefore, it is likely that patients with allergy did not efficiently handle RV infection. These processes might enable more viral replications, severe infections and prolonged inflammatory responses in allergic patients, which, in turn, may result in more severe RV infection symptoms.

The RV infection induced that IL-4, IL-5 and IFN-γ increased significantly in infected tissue from non-allergy group. In addition, the IL-4/IFN-γ ratio was increased after RV infection in non-allergy group, which suggests that the possibility of non-allergic subjects to have an increased risk of becoming Th2 biased environment after repeated rhinovirus infection. In allergy group, the IL-4/IFN-γ ratio did not significantly change.

Conclusions

Allergy and non-allergy subjects have a similar degree of susceptibility to RV infection.

Infected tissue from allergy exhibit significantly increased PD-L1 and IL-10. While, in non-allergy group, RV infection induced significantly higher level of IL-4, IL-5 and IFN-γ than its control. In addition, the IL-4/IFN-γ ratio was increased after RV infection in non-allergy group.

Enhanced PD-L1 and IL-10 cannot efficiently handle the immune response to RV, and it is more likely induce severe cold symptoms in allergic patients. Furthermore, elevated of IL-4/IFN-γ ratio in infected tissue from non-allergy group suggests that repeated rhinovirus infection may cause Th2 biased environment.

References


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