Inverse Expression of Fas Ligand and Asthma-Related Cytokines in an Aspergillus Challenge Murine Model of Asthma

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Abstract

Background: Asthma is a disease of chronic inflammation as well as hyperresponsiveness of the airways. Airway inflammation in asthma is characterized by initiation and maintenance of inflammatory cells followed by resolution. Fas ligand may act as an endogenous anti-inflammatory molecule in asthma by promoting the apoptosis of inflammatory effector cells such as eosinophils and lymphocytes. In previous experimentation, anti-Fas, given systemically or mice appeared to potentiate eosinophilic inflammation in a murine model (Almeida et al, Am J Respir Crit Care Med 2006; 174: A340). This would seem to implicate locally generated FasL in the clearance of pro-inflammatory cells. In this study we investigated the expression of asthma-related cytokines in the context of FasL protein and gene expression in an established Aspergillus mouse model of asthma.

Methods:
- BALB/c mice were sensitized and challenged with an Aspergillus fumigatus extract, and sacrificed 1, 7 and 10 days later to capture events during the inflammatory response and its resolution. Endpoints included bronchoalveolar lavage (BAL) cell counts, protein array analysis of BAL fluid, and cytokine gene array of total lung RNA.
- BAL eosinophilia peaked on day 1 and was associated with a marked increase in both Th1 and Th2 type cytokines including IL-12, IFN-γ, IL-4, IL-5, IL-6, and IL-10 and eosinophil-active chemotactic factors. In contrast, FasL protein and gene expression was suppressed at this time point compared to baseline. Resolving eosinophilia was coincident with a marked increase in FasL expression and the return of most cytokines toward baseline although residual chemokine levels were noted 10 days after allergen challenge.

Results:
- There was an inverse relationship between the expression of FasL and asthma-related cytokines. FasL protein levels were inversely correlated to the levels of typical asthma-related cytokines and were not observed in naive mice.
- We observed an inverse relationship between expression of FasL and asthma-related cytokines in an experimental asthma model. These data are consistent with a regulatory role for FasL during resolution. While Th2 cytokines are thought to orchestrate the initial response to antigen, multiple classically anti-inflammatory cytokines appear to be involved as well.

Summary/Conclusion

We hypothesize that active mechanisms, including anti-inflammatory cytokines and pro-apoptotic factors such as FasL, are involved in the resolution of inflammation in asthma.

Questions
- What is the relationship between local lung cytokine expression and resolution of inflammation?
- What is the relationship between local lung cytokine expression and FasL protein and gene expression?