Response to Comment on "A Novel Pathway That Regulates Inflammatory Disease in the Respiratory Tract"

Naiqian Niu and Lauren Cohn

*J Immunol* 2007; 178:7501-7502; doi: 10.4049/jimmunol.178.12.7501-a

http://www.jimmunol.org/content/178/12/7501.2

References

This article cites 7 articles, 2 of which you can access for free at:
http://www.jimmunol.org/content/178/12/7501.2.full#ref-list-1

Subscription

Information about subscribing to *The Journal of Immunology* is online at:
http://jimmunol.org/subscription

Permissions

Submit copyright permission requests at:
http://www.aai.org/About/Publications/JI/copyright.html

Email Alerts

Receive free email-alerts when new articles cite this article. Sign up at:
http://jimmunol.org/alerts
Comment on “A Novel Pathway that Regulates Inflammatory Disease in the Respiratory Tract”

In their recent article, Niu et al. (1) investigate the waning of allergic airway inflammation observed in mice repeatedly exposed to inhaled Ag. Using RAG1−/− mice, they show that the immune suppression resulting from administering inhaled Ag during both Th1- and Th2-mediated inflammation is not the consequence of actions by a regulatory T cell (Treg) population.

We recently obtained results providing further support for the notion of Treg-independent disease inhibition in mouse models using continued challenge with inhaled Ag. We found that mice with allergic airway inflammation, when continuously challenged, displayed an Ag-nonspecific and long-lasting disease inhibition (2). When we traced the evolution of the amount of CD4+CD25+Foxp3+ T cells in the lung during this process, we found that both the relative and the absolute number of these cells were down-regulated in the state of immune suppression compared with acute inflammation. This shows that the disease inhibition or “tolerance” did not critically depend on the number of Tregs, in contrast with the situation found in primary inhalational tolerance (3). Although this finding does not provide definite proof of a Treg-independent mechanism, we argue that our findings at least suggest it.

Niu et al. found the inhibitory effects to be associated with a population of TGF-β1-expressing macrophages, while we found alterations in the communication between dendritic cells and T cells. Nevertheless, no clear causal factor (meeting Koch’s postulates) was identified in both studies. Therefore, more research is needed to further characterize and identify the potent immune-suppressive mechanisms that underlie the observed waning of inflammatory disease.

Chris L. Van Hove, Tania Maes, Guy F. Joos, and Kurt G. Tournoy

Department of Respiratory Diseases
Ghent University Hospital
Ghent, Belgium

References


Response to Comment on “A Novel Pathway That Regulates Inflammatory Disease in the Respiratory Tract”

In sensitized animals that are repeatedly exposed to inhaled Ag, airway inflammation wanes over time. This regulatory effect has been observed for many years in different species, and it limits the development of chronic airway disease (1–6). We speculate that this type of regulatory pathway may also limit airway inflammation in healthy humans. To specifically define the components necessary for this regulatory effect, we developed a model that allows us to eliminate host T cell responses, yet still stimulate Th-induced inflammation using adoptively transferred, in vitro-generated Th cells. Thus, using RAG−/− hosts, we showed we can induce T cell inhibition (1). These studies convincingly demonstrate that immune regulation induced by repeated exposure to inhaled Ag during inflammation is not regulatory T cell (Treg) mediated. We are encouraged to see that our data are supported by Van Hove’s study (5), showing that Treg numbers inversely correlate with inhibition of inflammation. In our model, we avoid the use of the term “tolerance” since this effect is not mediated by T cells, and we call it “airway inflammation-related inhibition of disease (AIRID).”

Our model tests for inhibition of effector Th responses, whereas Van Hove et al. and others (3, 5, 7) use models that test for inhibition of primary immune responses. Thus, at present, we must be cautious not to assume we are studying the same pathway of inhibition. That aside, many features of these models are similar, including the Ag-nonspecific inhibitory effect.

Comparable to findings of Van Hove et al., our studies also revealed differences in activation markers on lung dendritic cells (DCs) from mice with acute inflammation compared with mice with inhibition of disease (our unpublished data). In AIRID, we suspect that these effects result from reduced inflammation in the lung environment, rather than being a cause of reduced inflammation. After repeated inhaled Ag exposure, we test for inhibition by challenging mice with adoptively transferred, recently in vitro-activated effector Th cells. In this system, inhaled Ag is only required for Th recruitment, not for Th proliferation. We expect that Ag-APC-T cell interactions required to provide signals for recruitment are fairly promiscuous, compared with the stringent signals required for naive T cell activation. The fairly subtle alterations in DC activation markers we have observed are unlikely to block Th cell recruitment to the lung. If recruitment was blocked, we might expect to observe Th cells elsewhere in the body, which we did not. More likely, the reduction in activation markers on lung DCs results from the marked diminution in lung inflammation.

We show that AIRID is associated with a population of TGF-β1+ macrophages. We hypothesize that repeated exposure to
inhaled Ag during inflammation activates a population of suppressive macrophages that directly and potently inhibits Th cells. Studies that are ongoing in the laboratory support this hypothesis.

Naqian Niu and Lauren Cohn

Section of Pulmonary and Critical Care
Yale University School of Medicine
New Haven, CT 06520

References


