

Impact of IL-6 in Allergic Asthma with

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What is the influence of IL-6 on the Th2 cells in allergic asthma?

Susetta Finotto: In initial studies on IL-6 signaling in asthma, we observed an increased production of soluble IL-6R (sIL-6R) in the bronchoalveolar lavage fluid (BALF) of patients with allergic asthma at baseline as compared to control subjects and a further increase after allergen challenge. Interestingly, sIL-6R levels strongly correlated with the number of CD4⁺/IL-5 producing cells, IL-5 and IL-13 in BALF of asthmatics after allergen challenge suggesting that sIL-6R levels contribute to Th2 cell development in asthma (1). We thus selectively blocked either the sIL-6R via gp130Fc or the soluble plus the membrane bound forms of the IL-6R via anti-IL-6R antibodies during the challenge phase, in a murine model (2,3). In the first therapeutical approach, we used a chimeric gp130Fc fusion protein that competes with gp130 and thereby specifically blocks IL-6 trans-signaling. Consistent with the above data in humans, it was found that specific suppression of sIL-6R signalling, via administration of gp130Fc, suppressed fully developed Th2 T cells in experimental asthma

in vivo. Collectively, these data indicate an important role for IL-6 trans-signaling via the sIL-6R in controlling Th2 T cell function in asthma. In contrast to gp130Fc treatment, local administration of anti-IL-6R antibodies led to the selective downregulation of IL-4, induction of IFN-gamma production by lung CD4⁺ T cells and amelioration of airway hyperresponsiveness suggesting the existence of important IL-6 dependent but sIL-6R independent signaling events at the beginning of Th2 differentiation in the lung in experimental asthma. These results are consistent with a Th2-promoting potential of pulmonary DCs due to the inhibition of Th1 differentiation caused by IL-6 production (4). Moreover, we identified the membrane bound IL-6R as being responsible for the Th1 inhibition since blockade of the IL-6R with antibodies induced significantly IFN-gamma in the airways. By contrast the soluble form of the IL-6R might control the number of fully developed Th2 cells since IFN-gamma was not induced by this treatment.

Are dendritic cells the main source of IL-6 in allergic asthma?

Susetta Finotto: IL-6 is produced by antigen presenting cells (APCs) such as B cells, macrophages, and dendritic cells. It can also be secreted by non professional APCs such as glial, epithelial, endothelial cells, fibroblasts and it is involved in the differentiation of B cells and myeloid cells (5). The receptor complex mediating the biological activities of IL-6 consists of two distinct membrane-bound glycoproteins, a cognate receptor subunit (alphaIL-6R) and a 130 kDa

signal-transducing element (gp130). In contrast, to the ubiquitous expression of gp130, cellular distribution of the cognate alphaIL-6R is limited to hepatocytes and some leukocyte subpopulations. It has been proposed that newborn infants have an immune-system dominated by Th2 cells than can be sustained when genetically predisposed subjects are exposed to a germ-free environment (Hygiene hypothesis). However, it is not entirely clear which factors are responsible for

priming T cells to differentiate into Th2 effector cells in allergic asthma. In this respect, IL-6 has been recognized to be important because it is secreted by cells of the innate immunity (antigen presenting cells, mast cells) and induces the expansion of the Th2 effectors cells, major

players of the adaptive immune responses (6,7). Moreover, IL-6 is a survival factor for resting T cells, not for activated CD4⁺ T cells. Finally IL-6 and other unidentified factors produced by mDC, are able to break CD4⁺ CD25⁺ T regulatory cell anergy and T cell proliferation (8).

How can IL-6 control the survival of CD4⁺CD25⁺ cells?

Susetta Finotto: It has been recently demonstrated that the activation of the innate immune system via Toll Like Receptors (TLRs) can block the suppressive effect of CD4⁺CD25⁺ Treg cells, allowing activation of pathogen-specific adaptive immune responses. This block of suppressor activity is dependent in part on IL-6, which was induced by TLRs upon recognition of microbial products (8). We therefore reasoned that IL-6, which is increased in the airways of asthmatic subjects, can induce Th2 cells in the lung also by suppressing CD4⁺CD25⁺ Foxp-3⁺ T regulatory cells in the airways. To test this hypothesis we analyzed cytokines in BALF and found that local blockade of membrane bound IL-6R via treatment with anti-IL-6R antibodies, but not blockade of the soluble IL-6R, through local treatment with gp130Fc, was associated with significant induction of IFN-γ and IL-10 levels in the BALF and lung CD4⁺ T cells supernatants of allergen sensitized mice. These results are consistent with previous reports showing enhanced ability of pulmonary DCs isolated from IL-6/- mice to induce a Th1 response. In fact, we found that a blockade of IL-6R led to an upregulation of

T-bet, the Th1 signature transcription factor in lung CD4⁺ T cells. Furthermore, we demonstrate that IL-6 signaling controls the balance between effector and regulatory T cells in experimental asthma by means of different receptor components. Specifically, our data suggest that IL-6 trans-signaling via the soluble IL-6R supports lung Th2 T cell cytokine production, whereas IL-6 signaling via the membrane bound IL-6R suppresses the development and functional activity of Foxp3⁺ regulatory CD4⁺CD25⁺ T cells in the lung and induces the early development of lung naïve CD4⁺ T cells via IL-4. Consistent with this concept, blockade of mIL-6R signaling induced expansion and immunosuppressive capacities of lung CD4⁺CD25⁺Foxp-3⁺ regulatory T cells *in vivo* and induced CD4⁺ IFN-gamma producing cells in the lung ameliorating AHR in experimental asthma. In addition, we demonstrated that the IL-6R is expressed and is functionally active in CD4⁺CD25⁺ T cells, since we have shown phosphorylation and activation of STAT-3 upon culture of these cells with IL-6, that is inhibited by anti IL-6R antibody co-incubation.

Is the inhibition of the IL-6 receptor a potential therapeutical tool?

Susetta Finotto: IL-6 signaling in the lung tightly controls the critical balance between effector and regulatory T cell function via differential signaling events involving sIL-6R and mIL-6R, respectively. Although our data are obtained from an experimental model of asthma, they suggest a potential therapeutic utility of local treatment with antibodies to the IL-6 receptor, for the local induction of T regulatory responses in patients with allergic asthma. Moreover this treatment can redirect CD4⁺ T cells into the Th1 pathway.

In addition, the fusion protein gp130Fc could be used as an anti-inflammatory therapy to neutralize sIL6R which is increased during airway inflammation. This would lead to amelioration of inflammatory symptoms because it directly targets fully developed Th2 cells in the airways.

REFERENCES

1. Doganci A et al. J Clin Invest 115, 313, 2005
2. Finotto S et al. J Exp Med 193, 1247, 2001
3. Rose-John S Acta Biochim Pol 50, 603, 2003
4. Dodge IL et al. J Immunol 170, 4457, 2003
5. Broide DH et al. J Allergy Clin Immunol 89, 958, 1992
6. Eisenbarth SC et al. J Exp Med 196, 1645, 2002
7. Rincon M et al. J Exp Med 185, 461, 1997
8. Pasare C et al. Science 299, 1033, 1993