ASTHMA-IL-17: Immunoregulatory functions of IL-17 and iNKT cells : new therapeutical approaches for allergic asthma

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Scientific Background and rationale

Allergic asthma has increased dramatically in prevalence and severity over the past two decades. It is well established by now that Th2 cells play a critical role in the pathogenesis of this disease. Nevertheless, the underlying immunological mechanisms remain poorly understood. The partners of this project (M. Leite-de-Moraes', B. Ryffel's and G. Eberl's teams), have recently contributed to new insights in this field of research by demonstrating the critical influence of the IL-17 and iNKT cells on the severity of experimental allergic asthma. In addition, a particular subset of iNKT cells can produce IL-17 upon stimulation, designing them as a potential source of IL-17 and a possible factor of disease aggravation. We proposed to extend this study by identifying the cells responsible for IL-17 production and to address the mechanisms of interaction between iNKT cells and IL-17, aiming at new approaches to inhibit asthma pathogenesis by targeting these players specifically.

Description of the project methodology

First, we identified IL-17-producing cells at different time points after immunization and challenge. This study was performed using mice with genetically modified DNA encoding a GFP reporter under control of the Rorc(γt) gene. These mutants were useful for the detection of IL-17-producing cells, knowing that they express the nuclear hormone receptor RORgt. The proportion of iNKT cells among RORγt-GFP+/IL-17+ cells in asthmatic mice were determined after labeling with CD1d/α-GalCer tetramers, which are specifically recognized by this population. Once we have identified IL-17 producer cells, we used adoptive transfer experiments to evaluate how they affect the severity of experimental allergic asthma. A classical experimental allergic asthma protocol consisting in the sensibilisation and challenge of mice with the ovalbumin (OVA) antigen was used along with this project. In brief, mice were systemically injected with OVA and further challenged intranasaly with OVA or NaCl (negative control). Asthmatic symptoms, such as lung inflammation and hyperreactivity, were then analyzed.

Results obtained

We performed the phenotypic and functional characterization of IL-17-producing T cells in asthmatic mice. First, we identified a more specific marker for the IL-17-producing iNKT (iNKT17) cells, the molecule ROR-γt. Later, we demonstrated that the number of iNKT17 cells is enhanced in the lung of asthmatic mice compared to controls. These cells were capable to amplify the major symptoms of allergic asthma. In addition, we also reported the implication of IL-17 in another model of lung injury and the cross-talk between IL-17 and IL-22 in allergic asthma.

Results obtained are reported in 4 scientific papers, described below. In addition, our findings are included in the PhD thesis of 3 students.

Michel, M. L., D. Mendes-da-Cruz, A. C. Keller, M. Lochner, E. Schneider, M. Dy, G. Eberl, M. C. Leite-de-Moraes. 2008. Critical role of ROR-gammat in a new thymic pathway leading to IL-17-producing invariant NKT cell differentiation. *Proc Natl Acad Sci U S A* 105:19845-19850.

Gasse, P., N. Riteau, R. Vacher, M. L. Michel, A. Fautrel, F. di Pavona, L. Fick, S. Charon, V. Lagente, G. Eberl, M. Le Bert, V. F. J. Quesniaux, F. Huaux, M. Leite-De-Moraes, B. Ryffel, I. Couillin. submitted. IL-1 and IL-23 mediate early IL-17A production by gd T cell in pulmonary inflammation and fibrosis.

Massot, B., C. Brochetta, S. Diem, M. L. Michel, A. G. Besnard, T. Secher, I. Couillin, B. Ryffel, G. Eberl, M. Dy, M. Leite-De-Moraes. submitted. RORgtpos iNKT cells promote mucus production and airway hyperreactivity exacerbation in experimental allergic asthma.

Besnard, A. G., R. Sabat, L. Dumoutier, J. C. Renauld, M. Willart, B. Lambrecht, M. M. Teixeira, S. Charron, L. Fick, F. Erard, K. Warszawska, K. Wolk, V. Quesniaux, B. Ryffel, D. Togbe. 2011. Dual Role of IL-22 in Allergic Airway Inflammation and its Cross-Talk with IL-17A. *Am J Respir Crit Care Med*.

Conclusions

We have answered the major questions of the project : we identified the source of IL-17 in the lung of asthmatic mice and we demonstrated that IL-17-producing iNKT cells (iNKT17) are implicated in the severity of experimental allergic asthma. Our results suggest that IL-17-producing iNKT cells may be implicated in severe allergic asthma in humans. However, further studies are required to test this hypothesis.

In conclusion, during this project our three teams worked together and obtained original findings that add new clues to the understanding of the complex contribution of iNKT cells and IL-17 to the pathogenesis of allergic asthma.

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