# ACTIVATION/DEACTIVATION OF MACROPHAGES AND CD4+ T LYMPHOCYTES IN EXPERIMENTAL ASTHMA

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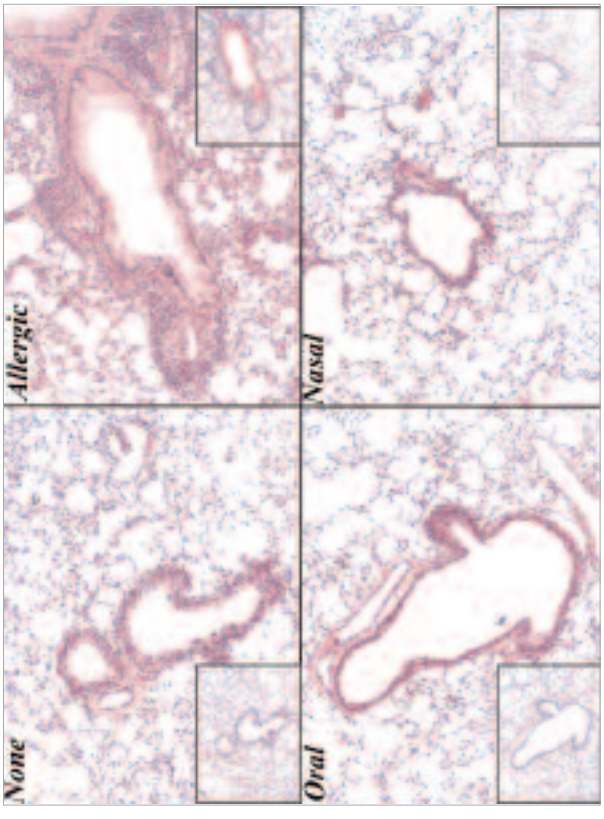


*Modulation of experimental asthma by oral or nasal olerance. The figure shows lungs of healthy, allergic and animals treated with allergens by oral and nasal route*

Over the last 2 to 3 decades, the prevalence and severity of asthma and allergic disease has increased extensively in urban environments. The "hygiene hypothesis" was proposed in order to explain this increased incidence. This hypothesis is based on epidemiological evidence showing an inverse correlation between infections and allergic or autoimmune diseases. Recently, it was proposed that infections generate regulatory T cells that inhibit allergic (Th2) or autoimmune (Th1) diseases. Accordingly, the control of infectious diseases in urban environments decreased Treg cells activities that lead to a deregulated immune system. Various Treg cells has been characterized, natural Treg (CD4+ CD25+ CD45RB low) which inhibit aureactive T cells and adaptive Treg, that inhibit Th1- or Th2-mediated immune reactions. The adaptive Treg are heterogeneous cell population, but natural Treg cells are CD4+ CD25+ and the majority expresses the transcription factor Foxp3. One objective of the project is to investigate whether Treg induced by oral or nasal tolerance, or by recombinant BCG infection, or LPS would suppress the development of asthma. Another possibility for the suppression of asthma by infections is the emergence of activated macrophages. Recently, we have shown that i.v. administration of LPS suppresses established asthma. The suppressive activity was dependent on TLR4 and NOS2 expression and NO production. It is possible that other metabolites produced by activated macrophages such as those derived from indolamine, 2,3 dioxigenase or hemeoxigenase 1 pathways may also suppress asthma. For this purpose we will test some classical TLRs agonists (PIC, LPS or rBCG), or a synthetic TLR4-agonist on the development of asthma with focus on these metabolic pathway.

## SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Usually, the immune system protects against a variety of noxious agents. However, in certain circumstances it can cause disease. Some immunological disorders are due to a polarization of T helper cells that can be characterized as Th1 or Th2 cells. Th1 cells are involved in autoimmune diseases such as Crohn's disease and arthritis, while Th2 cells mediate allergic processes such as atrophy and asthma. Experimentally, it is possible to reproduce these diseases using different types of adjuvants. Our focus is to understand the modulation of Th2 polarized allergic response, using essentially a murine model of asthma, either by interfering with the adjuvant activity or by manipulating the immune system through immunological tolerance or microbial products.

We have shown that the asthma-like responses could be down modulated by interfering in the adjuvant activity of Alum, the most commonly used adjuvant in human vaccination and a prototypic Th2 adjuvant (Bortolatto, 2008). In another work, we showed that the acute phase protein, serum amyloid A could be a TLR4 agonist, or a Th1 adjuvant (Sandri, 2008). Taken together, our work opens the possibility of using a combination of adjuvants to induce protective immune responses without polarization. We also showed that natural products such as the plant *Lafoensia pacari* have anti-inflammatory activity in our asthma model (Rogerio, 2008). Another line of investigation deals with immunological tolerance that is achieved by the administration of allergen via mucosal surfaces (Keller, 2006 and Mucida 2005). We also determined the repercussions of allergy on brain activity. We showed that the brain and behavior are modified by allergic responses (Costa-Pinto, 2007). Finally, products of activated macrophages might be key elements in suppressing allergic responses (Keller, 2005). The impact of our work was acknowledged in a recent publication in *Nature Review Immunology* (March 2008) dealing with allergy.

## MAIN PUBLICATIONS


Bortolatto J, Borducchi E, Rodriguez D, Keller AC, et al. Toll-like receptor 4 agonists adsorbed to aluminum hydroxide adjuvant prevent ovalbumin-specific allergic airway disease. *Clinical & Experimental Allergy*. Em revisão final, Março 2008.

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