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Deficiency of regulatory B cells in a house dust mite model of asthma

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Introduction

Asthma is a chronic disorder leading to bronchial obstruction in response to inhaled allergen. It is associated with immune deregulation with specific expansion of Th_2 and Th_{17} $CD4^+$ T cells. Both T cell populations support B cells response by stimulating their proliferation, survival and IgE secretion. B cells are described for their effector functions but recently reports have described their regulatory role in autoimmune and inflammatory disorders. However, definitive identification has been challenging because regulatory B cells (Breg) are rare, do not have a specific marker, and express detectable IL-10 or TGF-β only upon *ex vivo* stimulation. In OVA asthma models, local inhalation tolerance [1], [2] and infections with helminthes [3], [4] induce the generation of regulatory B cells. But no physiological role of this population in the development of asthma has been described yet.

Methods

Mice were sensitized on days 0, 7, 14 and 21 by percutaneous administration of HDM onto the ears. Intra-nasal challenges were performed on day 27 and 34 with 250 μg HDM. One day after each challenge, we realized by flow cytometry a complete B cell phenotyping in spleen and lungs.

Splenocytes and lung cells were isolated and stimulated *ex vivo* with LPS and PMA, ionomycin to induce IL-10 secretion by B cells.

Results

No differential frequency was observed for all B cell populations in the spleen of HDM allergic mice, suggesting a normal B cell development. In contrast, HDM allergic mice exhibit a strong infiltration of $CD19^+$ B cells in lungs and broncho-alveolar lavage after the second challenge. We found an increase of CD19 IgD^{hi} IgM^{low} B2 mature and CD19 IgD- IgM- switched memory B cells in the lung of HDM allergic compared to control mice. We looked at $CD19^+$ IL-10^+ $CD1d^{hi}$ $CD5^+$ $CD21^+$ $CD24^{hi}$ IgM^{hi} B cell population that has been shown to display regulatory properties in other situations. Whereas this population is present in spleen and lungs of HDM allergic mice, it produces less IL-10 than control after the first and the second challenge both in lung (vs control, $p<0.01$) and spleen (vs control, $p<0.05$).

Conclusions

Our results strongly suggest a potential defect of regulatory B cells in the course of asthma. Future investigations will focus on their capacities to inhibit bronchial hyperreactivity and inflammatory responses.

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