Editorial
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Immunomodulating Approach to Asthma Using Mycobacteria

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Asthma is characterized by chronic inflammation of the airways, and inhaled steroids (ICSs) currently represent the most effective anti-asthma medication. However, due to the potential side-effects of long-term use of ICSs, the recurrence of asthma soon after the withdrawal of ICSs, and the refractoriness of airway remodeling to ICS treatment, other approaches for the control of asthma are needed. The current concept of asthma pathogenesis is that pathogenic immune responses to common respiratory exposure in vulnerable individuals result in persistent inflammation and aberrant repair processes in the airways. Therefore, early intervention during the developing stages of this intractable disease would present the best strategy for managing asthma. Moreover, cellular components, such as dendritic cells (DCs) active during the developing stage, continuously affect the chronic airway inflammation in asthma, even without further exposure to the relevant allergens. Thus, interventional approaches to modulate the early pathogenic immune response, such as allergen-specific immunotherapy, anti-IgE monoclonal antibody (omalizumab), probiotics, and Bacillus Calmette-Guérin (BCG) vaccination appear to work in preventing the development of asthma, and in treating established asthmatic disease.

In 1997, Shirakawa *et al.*[1] reported an inverse association between tuberculin skin responses and atopic disorder. Further epidemiologic studies revealed an association between tuberculosis[2] or BCG vaccination[3,4] and reduced prevalence of asthma or allergy. Because BCG is less virulent than *Mycobacterium tuberculosis*, the efficacy of the BCG vaccination in asthma prevention is lower than that of active tuberculosis, and only lasts for 2 years.[5] As the article by Kim *et al.*[6] published in this issue, many animal studies have demonstrated the preventive or therapeutic effects of BCG vaccination on asthma.[7,8] In this context, we performed a double-blinded placebo-controlled human study in 2002, and demonstrated that BCG vaccination improved lung function and reduced medication-use in adult asthmatics.[9] In subsequent studies, BCG revaccination further improved lung function,[10] and the greatest benefit occurred in young asthmatic women.[11]

The scientific basis for the so-called 'hygiene/old friend hypothesis,' initially proposed in 1989 by Strachan,[12] suggested that improved sanitation decreased infection and the production of Th1 cytokine interferon (INF)-γ, resulting in a shift of the Th1/Th2 balance to increase Th2-associated disease. However, in 2002 Bach[13] demonstrated that this decrease in infection was accompanied by an increase in the prevalence of Th1-driven autoimmune diseases, as well as in allergic diseases over recent decades.[13] Umetsu *et al.*[14] proposed that the main mechanism underlying the hygiene hypothesis would be related to a failure of regulatory T (Treg) cell development, resulting in a loss of tolerance to allergens. Regarding to BCG vaccination, Zuany-Amorim *et al.*[15] showed that *Mycobacterium vaccae* induced Treg cells to produce interleukin (IL)-10 and transforming growth factor (TGF)-β. In addition, Li and Shen[16] demonstrated that BCG prevented the development of allergic inflammatory responses and increased the proportion of $CD4^+CD25^+$ Treg cells, Foxp3 expression, and the production of IL-10 and TGF-β in the spleen. Kim *et al.*[6] also demonstrated that anti-CD25 monoclonal antibody pre-treatment abrogated the anti-asthmatic effects of BCG. However, mycobacteria, including BCG, are well-known potent inducers of Th1 responses.[17] The representative Th1 cytokine IFN-γ apparently suppresses the asthmatic airway responses when administered for a short duration.[18] Therefore, IFN-γ production (immune deviation) by BCG seems to play an important role in suppressing asthma, at least initially, even though immune suppression through Treg cell-induction appears to be the main mechanism involved.

The adaptive immune response to allergens and mycobacte-

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ria is initiated by DCs. Pattern recognition receptors, including Toll-like receptors (TLRs), on the surface of the DCs recognize foreign material and phagocytose it, or transduce signals into the DCs. T cell receptors recognize the presented fragments of the foreign material on MHC class II of the DCs (signal 1), and co-stimulatory molecules, such as CD80/86 expressed on the cell surface of activated DCs, interact with ligands (such as CD28) on the T cell surface (signal 2). At the same time, polarizing molecules, such as IL-12 produced by DCs (signal 3), determine the type of T cell responses needed. Mycobacterial products are recognized by TLR2 and TLR4, which lead to secretion of IL-12 and IL-10 from DCs, and the development of Th1/Treg cells.[19] MBP70, a major secreted protein of BCG,[20] and mycolic acid, a cell-wall component of BCG,[21] effectively suppressed asthmatic reactions in murine models. Although the findings by Kim *et al*.[6] are rare one showing a suppressive effect of BCG-treated DCs on asthma, live BCG vaccination and administration of BCG-treated DCs naturally work in the same manner, because BCG produces adaptive immunity through DCs. Further research using mycobacterial product-pulsed DCs or DCs co-cultured with allergens and BCG is needed. Co-administration of *Dermatophagoides farinae* and BCG to DCs increased the efficiency of IL-10 production from DCs, and effectively decreased IL-5 production from T cells,[22] probably because the allergen and BCG were simultaneously recognized by the same DCs. In addition, co-pulsing of DCs with unrelated antigens may have a mutual helper effect.[23]

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