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IL-23, rather than IL-17, is crucial for the development of ovalbumin-induced allergic rhinitis

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ABSTRACT

Interleukin-23 (IL-23) and IL-17 are involved in the pathogenesis of allergic rhinitis (AR). However, the roles of IL-23 and IL-17 in ovalbumin (OVA)-induced AR remain unclear. Therefore in this study we aim to investigate the precise roles of IL-23 and IL-17 in a mouse model of OVA-induced AR. We found that during OVA-induced AR, eosinophil and goblet cells in the nose were significantly decreased in IL-23-deficient, but not in IL-17-deficient mice. However, there was no difference in the serum IgE and IgG1 levels between IL-23-deficient or IL-17-deficient and wild-type mice. Moreover, IL-4 levels in lymph node cell culture supernatants were significantly decreased in IL-23-deficient, but not IL-17-deficient, compared with wild-type mice. Furthermore, OVA-induced AR developed similarly in wild-type mice transferred with either IL-23-deficient BM cells or wild-type BM cells. These findings suggest that IL-23, but not IL-17 is crucial for the development of OVA-induced AR, and IL-23 neutralization may be a potential approach for treatment of OVA-induced AR in humans.

1. Introduction

The prevalence of allergic diseases, including asthma, rhinitis, eczema, and food allergies, has risen sharply (Holgate, 1999). Allergic rhinitis, which is a condition similar to common cold, could affect mental and learning capacities up to 30% (Global Allergy and Asthma European Network addresses the allergy and asthma epidemic) (Bousquet et al., 2009). AR is an inflammatory disease of the nasal mucosa induced by an immunoglobulin E (Helbling et al., 2014)-mediated reaction in allergen-sensitized individuals. It has been reported that numerous loci and candidate genes show an association with AR (Gaddam et al., 2012; Genuneit et al., 2009; Ibrahim et al., 2012; Tomazic et al., 2014). In spite of that, the molecular mechanisms underlying the development of AR have not been completely determined.

Interleukin-IL-23 (IL-23), a heterodimeric cytokine consisting of a p19 subunit specific for IL-23 and a p40 subunit shared with IL-12, has been shown to play a significant role in the maintenance (Langrish et al., 2005) and acquisition of pathogenic function of Th17 cells (McGeachy et al., 2007). Whereas interleukin-17 (IL-17; also known as IL-17A) is a member of IL-17 cytokine family produced predominantly by a subpopulation of $CD4^+$ T cells, Th17 cells (Harrington et al., 2005). Indeed, IL-23-IL-17 link has been found to be associated with the development of various inflammatory diseases, such as psoriasis (Di Cesare et al., 2009), arthritis (Cornelissen et al., 2009) and inflammatory bowel disease (IBD) (Sarra et al., 2010). To date, studies in patients with AR indicate that IL-23 and IL-17 are also likely to be involved in the pathogenesis of this condition (Nieminen et al., 2010). However, the role of IL-23 and Th17 in the regulation of allergic airway inflammation remains largely unknown. Therefore, in this study, we aimed to determine the roles of IL-23 and IL-17 in the development of OVA-induced AR, using AR model by treating wild-type, IL-23-deficient and IL-17-deficient mice with OVA.

2. Materials and methods

2.1. Mice

Female CD45.1-C57BL/6J, CD45.2-C57BL/6J, CD45.1-C57BL/6N wild-type mice, IL-$23^{-/-}$-CD45.1-C57BL/6N, C57BL/6J-wild-type and IL-$17^{-/-}$ mice (6–8-week-old) were purchased from Shanghai SLAC Laboratory Animal Co., Ltd. (Shanghai, China) and were housed in the Animal Resource Facility. All procedures and experiments involving animals in this study were performed in

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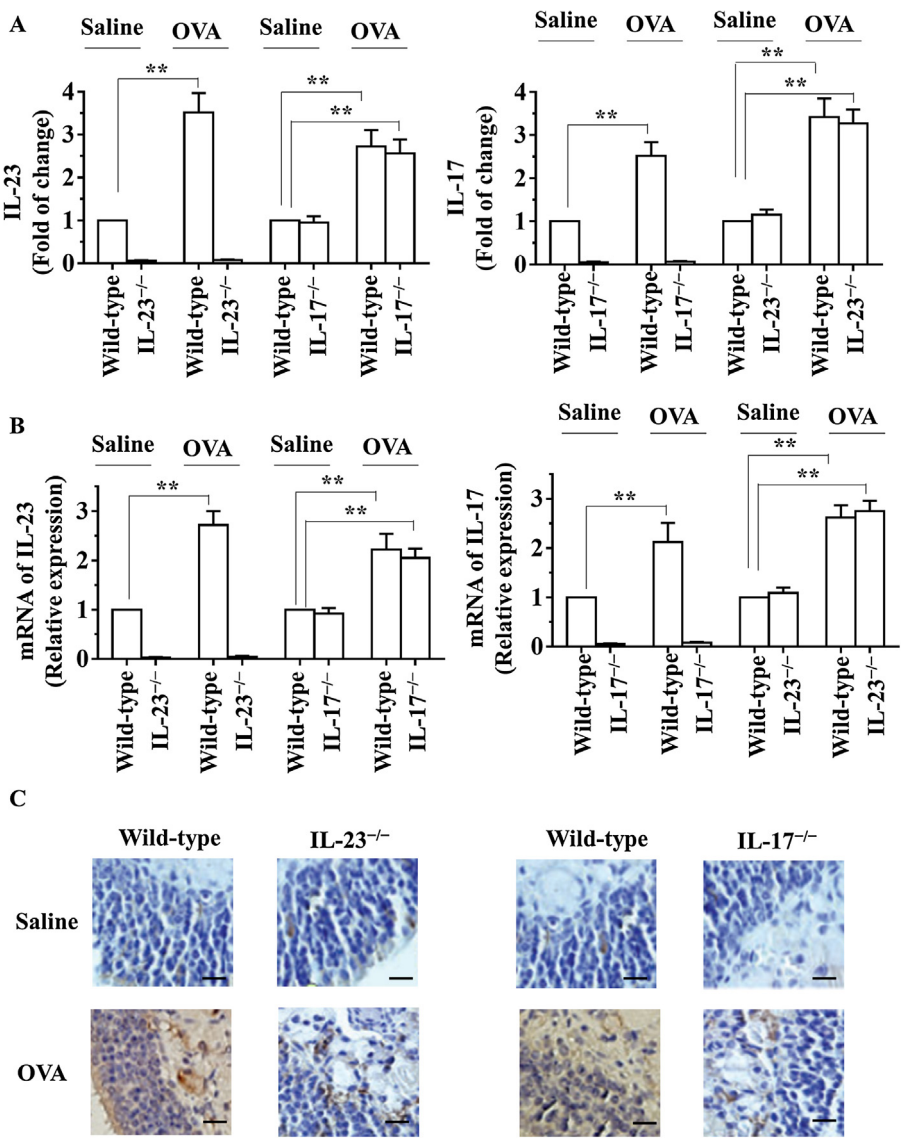

Fig. 1. Up-regulation of IL-23 and IL-17 in the mouse model of AR. (A and B) Blood and nasal mucosa were collected 24 h after the last challenge and analysed for serum IL-23 and IL-17 levels (A), relative mRNA level of IL-23 and IL-17 in nasal mucosa (B). (C) The sections were stained with anti-rabitt-IL-23 or anti-rabitt-IL-17 Abs. IL-23 and IL-17 were detected in the cytoplasm of epithelial cells (brown) from OVA-treated mice. Scale bars, 100 μm. Data are presented as the mean ± SD from 6 mice in each group ($n = 6$). ** $p < 0.01$, *versus* control. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

accordance with the National Institutes of Health Guide for Care and Use of Laboratory Animals. The protocol was approved by the Committee on the Ethics of Animal Experiments of Qingdao Municiple Hospital. All surgery was performed under sodium pentobarbital anesthesia, and all efforts were made to minimize suffering.

2.2. Mouse model of OVA-induced allergic rhinitis

The sensitization challenge for the murine model of AR was performed as previously described with slight modification (Saito et al., 2002). Under pathogen-free conditions, mice were sensitized using OVA (Sigma-Aldrich, St. Louis, MO, USA) as follows. Ovalbumin (40 μg/kg) OVA diluted in sterile normal saline was administered along with aluminum hydroxide gel (alum adjuvant, 40 mg/kg) to un-anesthetized animals four times by intraperitoneal injection on days 1, 5, 14, and 21. This was followed by daily intranasal challenge with OVA diluted with sterile normal saline intranasally (20 μL of 25 mg/ml OVA per mouse) from days 22 to 35. Twenty-four hours after the last OVA challenge, blood and tissues were collected from each mouse.

2.3. Bone marrow cell transfer

CD45.1-C57BL/6J mice were irradiated with X-rays (8 Gy) and then injected intravenously with bone marrow cells (2×10^7 cells) from CD45.2-C57BL/6N-wild-type or -IL-23$^{-/-}$ mice. One month later, the mice were used for experiments (CD45.2$^+$ cells >95% in the spleen by FACS).

2.4. Measurement of OVA-specific IgE and total IgE

Serum levels of total IgE and OVA-specific IgG1 were measured by solid-phase enzyme-linked immunosorbent assay (ELISA) in accordance with the manufacturer's instructions. Bound immunoglobulin isotypes were detected with specific secondary antibody (biotin-conjugated rat anti-mouse IgE and IgG1 Abs were purchased from BD Pharmingen, San Jose, CA, USA).

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