

IL-33 links tissue cells, dendritic cells and Th2 cell development in a mouse model of asthma

Thomas Eiwegger^{1,2} and Cezmi A. Akdis¹

¹ Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland

² Medical University of Vienna, Department of Pediatrics, Vienna, Austria

IL-33 is becoming a central molecule in allergic asthma that addresses various cascades of innate and adaptive immune responses that lead to inflammation in the lung. Its effects are exerted via its heterodimeric receptor that consists of ST2 and the ubiquitously expressed IL-1 receptor accessory protein (ILRAcP). IL-33 integrates both innate and adaptive immunity in a unique fashion via basophils, mast cells, eosinophils, innate lymphoid cells, NK and NKT cells, nuocytes, Th2 lymphocytes and a CD34^{pos} precursor cell population. These actions of IL-33 seem to be particularly strong and dominant in models with mucosal inflammation. A study in this issue of the *European Journal of Immunology* demonstrates that IL-33 acts, in an ST2-dependent manner, as a maturation factor for BM-derived DCs via up-regulation of CD80, CD40 and OX40L. This process is accompanied by the release of pro-inflammatory cytokines, such as IL-6, IL-1 β , TNF- α and TARC/CCL17. IL-33-pre-treated DCs were significantly more potent for the generation of allergen-specific Th2-type cells with IL-5 and IL-13 production. Intratracheal administration of OVA-pulsed DCs with IL-33 significantly enhances eosinophil numbers and mucous secretion. In conclusion, IL-33 affects both the development of allergic sensitization and the development of lung inflammation in allergic asthma.

Key words: Animal models • Asthma • Cytokines • DCs



See accompanying article by Besnard et al.

A better understanding of immune regulation in the context of various diseases is key to develop new disease-tailored therapeutic approaches. In particular, the epithelium as a cytokine producer itself and key player in the orchestration of inflammatory events still awaits closer investigation. Recent progress in understanding the interaction between immune/inflammatory cell subsets via interleukins, particularly reciprocal regulation and counter balance between Th1, Th2, Th9, Th17, Th22 and T regulatory cells, as well as B-cell subsets, bring new possibilities for immune intervention. With regard to allergic diseases, the

process of developing such diseases is characterized by effector Th2 cells that produce IL-4, IL-5, IL-9 and IL-13 [1–4]. In addition, recently defined cytokines, such as IL-25, IL-31, IL-32 and IL-33 that contribute to Th2 responses, tissue inflammation, allergen-specific IgE production, eosinophilia, mucous production, and the activation and cell death of the epithelium represent newly emerging and essential players in the pathogenesis of allergic inflammatory disease [5–9].

In the context of tissue-related allergy-driving factors, the IL-1 family member cytokine IL-33 is becoming a key player in the initiation and exacerbation of inflammatory responses. Its effects are exerted via its heterodimeric receptor that consists of ST2 and the ubiquitously expressed IL-1 receptor accessory protein (ILRAcP) [10]. IL-33 integrates both innate and adaptive

Correspondence: Prof. Cezmi A. Akdis
e-mail: akdisac@siaf.unizh.ch

immunity in a unique manner. It affects basophils, mast cells, eosinophils, innate lymphoid cells, NK and NKT cells and Th2 lymphocytes [2, 11]. In addition, IL-33 impacts CD34^{pos} precursor cell populations [12] and is involved in the activation of a cell subpopulation called nuocytes that are crucial for parasite repulsion. This nuocyte population was defined as lineage^{neg} ICOS^{pos} ST2^{pos} IL-17RB^{pos} and IL17Ra^{pos} cells and is considered to be an upstream Th2 inducer/amplifier, whose properties still remain to be defined in detail [7]. The actions of IL-33 seem to be particularly evident when looking at models of mucosal inflammation.

In this issue of the *European Journal of Immunology*, an article by Besnard et al. adds significant information regarding the role of IL-33 in the context of a mouse model of asthma-like lung inflammation [13]. The authors demonstrate that IL-33 acts, in an ST2-dependent manner, as a maturation factor for BM-derived DCs via up-regulation of CD80, CD40 and OX40L. This process is accompanied by the release of pro-inflammatory cytokines, such as IL-6, IL-1 β , TNF- α and TARC/CCL17. IL-33-pre-treated DCs were significantly more potent than non-treated DCs at inducing allergen-specific proliferation in naïve T-cells, and the generated T-cell responses were of a Th2 type with IL-5 and IL-13 production. This activation/maturation of lung resident DCs was also confirmed in vivo via local application of IL-33, inducing up-regulation of the homing receptor CCR7 in the CD11c^{pos} fraction.

The activated DC phenotype was observed in the draining LN, and PBMCs from the LN displayed a Th2 phenotype upon re-stimulation with anti-CD3/CD28. The in vivo relevance of IL-33 on DC maturation, eosinophil numbers and macrophage activation was confirmed in mice. Intratracheal administration of OVA-pulsed DCs with IL-33 significantly enhances eosinophil counts and mucous secretion in the lung as compared with OVA-pulsed DCs alone. Taken together, the data indicate that IL-33 affects DC maturation in the lung leading to DC migration to the lymph nodes, where they can thereby contribute to the priming of Th2 cells and the induction of allergic airway inflammation (Figure 1).

These findings are remarkable since they demonstrate a new effector cell population that significantly contributes to the IL-33-mediated effects, such as Th2 induction and eosinophil recruitment in the lung, processes that have not been well understood to date. Consequently, IL-33 may be an alarmin that integrates danger with a Th2-type response, thereby initially controlling the potentially overwhelming immune responses, such as those observed in sepsis [14]. However, IL-33 may also drive the immune system in the lung towards the development of allergen-specific Th2-type responses. Epidemiological and experimental data suggest a strong link between concomitant infection, in particular with rhinovirus and respiratory syncytial virus in the first year of life that may lead to obstructive

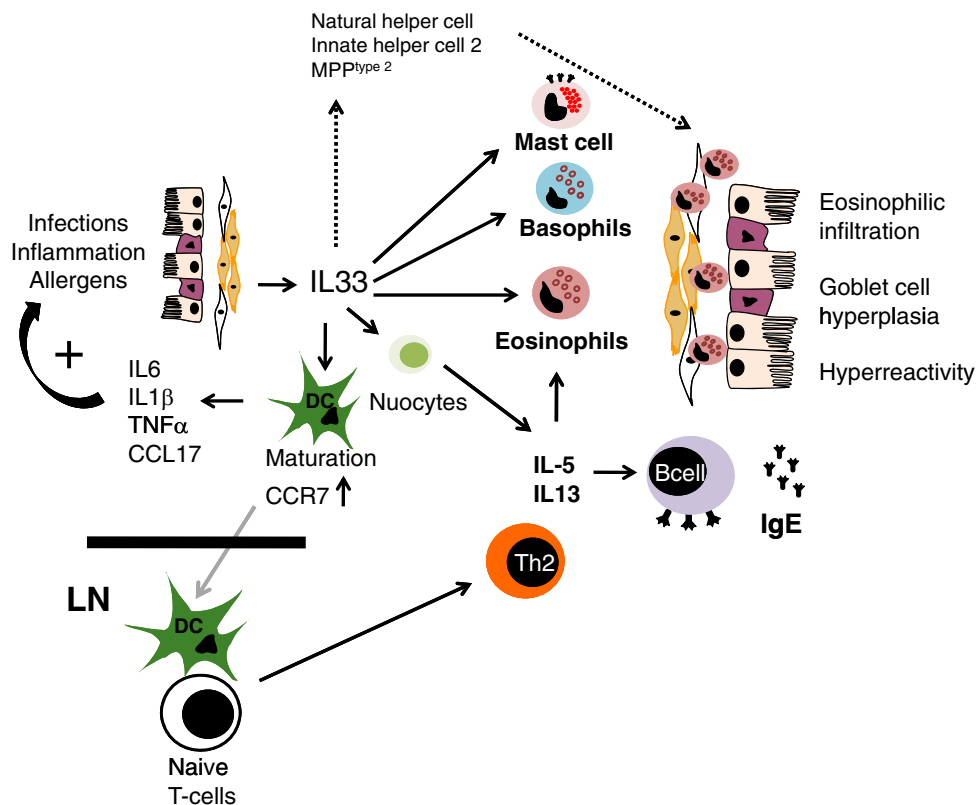


Figure 1. Release of IL-33 in the lung leads to the maturation of lung DCs and the induction of pro-inflammatory cytokines like IL-6, TNF- α , IL-1- β and CCL17 by this DC population. The matured DCs home to the LN, where they prime Th2 cells that drive allergic inflammation the lung.

bronchitis, and subsequent development of asthma [15]. DCs and alternatively activated macrophages are considered to be the key regulators of the initiation of an immune response and to be modulators of inflammation. Given the assumption that IL-33 is locally released in the lung via exogenous factors such as infections that lead to cell destruction and inflammation, it is tempting to speculate on the role of IL-33 in the induction of asthma, in particular in the context of virus-induced exacerbations of asthma; however, experimental evidences from models integrating both virus infection and IL-33 are still limited.

The IL-33 receptor ST2 was demonstrated to be an orphan receptor over a decade ago and has been linked to allergic diseases [5, 16]. It occurs in a membrane-bound form that is responsible for the IL-33-mediated functions, and in a soluble form that is considered to act as a scavenger receptor antagonizing ST2-mediated effects [17]. One of the main reasons for the late discovery of IL-33 may be the fact that it is not secreted in a conventional way. In fact, the circumstances of IL-33 release still remain enigmatic since active secretion has not been demonstrated. IL-33 is constitutively expressed in various tissue cells in the lung including smooth muscle cells, fibroblasts, endothelial cells and epithelial cells of mucosal surfaces. In contrast to IL-1 β , IL-33 is located in the nucleus in its active form where it is considered to exert repressor activities. The cleavage of IL-33 via caspases 3 and 7 leads to its inactivation [18]. Consequently, the release of IL-33 seems to be tightly linked to tissue damage and necrosis of epithelial cells. Apoptosis on the other hand may inactivate IL-33. It is likely that both inactivation and release of IL-33 take place linking between apoptosis and cell damage in many chronic inflammatory diseases in which IL-33 has been detected.

The crucial role of IL-33 in asthma has been assumed due to several pieces of evidence. Administration of IL-33 results in lymphocyte-independent airway hyperreactivity, goblet cell hyperplasia and eosinophilic and monocytic infiltration. Hyper trophy and enhanced mucous secretion in the bronchi and bronchioles occurs after repeated applications in mice [5]. In addition, IL-13-dependent differentiation of alveolar macrophages towards alternatively activated macrophages with increased airway inflammation has been reported in a murine model [19]. Furthermore, CD34^{pos} progenitor cells express the receptor for IL-33, ST2, and secrete large amounts of Th2-type cytokines and chemokines in the presence of IL-33. IL-13- and IL-5-expressing CD34^{pos} cells have been found in the sputum of asthmatic individuals and were up-regulated upon allergen-challenge [12]. Moreover, IL-33 contributes to the recruitment and activation of eosinophils to the same degree as IL-5. The in vivo relevance of IL-33 in human asthma is further supported by its higher expression in epithelial cells and smooth muscle cells in moderate to severe asthmatics, but not mild asthmatics. This has been confirmed at the protein level in bronchoalveolar lavage fluid [20]. Finally, a genome-wide association study has reported the association between single nucleotide polymorphisms in the IL-33 gene and in the ST2 gene and an increased risk to develop asthma [21].

In conclusion, IL-33 is evolving as a candidate molecule that acts on DCs and bridges innate and adaptive immune responses in the lung. IL-33 thereby affects both the development of allergic sensitization and the aggravation of lung inflammation. The study by Besnard et al. [13] demonstrates this in an elegant way, defining DCs as effector cells in vivo and confirming ST2-specific DC activation. However, further work is required to fully delineate the role of IL-33 in allergic disease.

Conflict of interest: The authors declare no financial or commercial conflict of interest.

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Full correspondence: Prof. Cezmi A. Akdis, Swiss Institute of Allergy and Asthma Research (SIAF), University of Zurich, Davos, Switzerland
 Fax: +41-81-4100840
 e-mail: akdisac@siaf.unizh.ch

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