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# Involvement of ion channels in allergy

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Allergic asthma is a complex disease, often characterized by an inappropriate Th2 response to normally harmless allergens. Epithelial cells damaged or activated by the allergen produce IL-33, TSLP and IL-25, activating ILC2 and dendritic cells. The latter migrate into lymph nodes where they induce Th2-cell commitment. Th2 and other type 2 innate inflammatory cells trigger inflammation and airway hyper-reactivity. The toolbox consisting of the ion channels varies from one cellular type to another and depends on its activation state, offering the possibility to design novel drugs in the field of allergy. We will discuss about some channels as calcium, nonselective cation, potassium and chloride channels that appear as good candidates in allergy.

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## Introduction

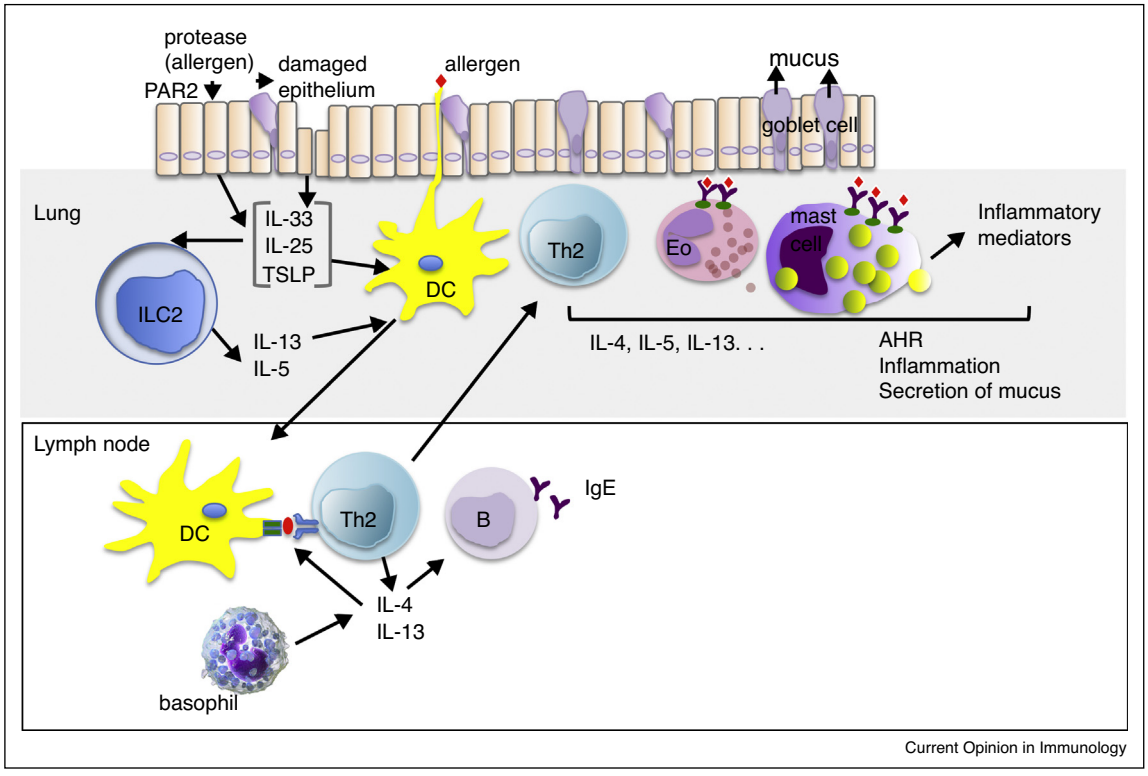
Allergy is initiated by an inadequate immune responsiveness to normally harmless airway allergens, occurring in genetically predisposed humans. The allergic diseases include atopic dermatitis, allergic asthma, and food allergies. We will focus on allergic asthma that affects more than 300 millions of people worldwide. This chronic pulmonary disease often starts during childhood and causes airway hyper-responsiveness [1••].

Antigen recognition induces the differentiation of naive T-cells into T helper cell effectors that include several subsets as Th1, Th2, and Th17. These populations express master transcription factors, produce a specialized pattern of cytokines and exert distinct functions. Th2-cells express the master transcription factor GATA-3 and are normally devoted to the eradication of parasites. We focus on this subset that produces interleukins (IL)-4, 5, 9, 13 and GM–CSF [2,3] because their role in allergy has been well demonstrated in experimental models of allergic asthma but also in humans. Dendritic cells (DCs) pick up the allergen in the lungs, get activated, maturate, and migrate into the draining lymph nodes where they induce Th2-cell commitment (Figure 1). IL-4 and IL-13 are implicated in immunoglobulin (Ig)E commutation switch by B-lymphocytes. IL-4 promotes Th2 differentiation through STAT-6 signaling and thus amplifies the pool of Th2-cells. Activated Th2-cells will migrate to the lungs where they contribute to inflammation. IL-5 promotes the differentiation of eosinophils (a hallmark of allergic diseases) and their recruitment into the lungs. IL-13 has a major impact on disease development (Figure 2) [4]. Indeed, it allows the recruitment of inflammatory cells into the lungs and acts on epithelial cells resulting in the production of chemo-attractants. IL-13 also enables the production of mucus by goblet cells, fosters bronchoconstriction and prevents NO-mediated muscle relaxation. It also acts on fibroblasts to promote TGFβ production and fibrosis.

An important issue is how Th2-cells are preferentially induced in allergic patients. There are several nonexclusive possible explanations. Allergy often develops in early infancy. At that time, lung structures are vulnerable to environmental injuries [5]. In addition, the immune system that is immature is skewed to Th2-response [6]. These factors contribute to the development of allergic asthma.

The nature of allergens is also of concern. Indeed, they have often protease activity, inducing epithelial damage and alteration of the epithelial barrier but they also target the production of chemokines, IL-25, 33 and TSLP by epithelial cells [7] (Figure 1). These cytokines have at least three roles. First, they instruct DCs to promote Th2-cell differentiation. One important clue is the expression of the cluster of differentiation CD134 (OX40 ligand) and the absence of production of IL-12 by DCs [8,9•]. Second, they activate type 2 innate lymphoid cells (ILC2) that express the transcription factors GATA-binding protein (GATA)-3 and the retinoic acid-related orphan receptor (ROR) α. ILC2 share many properties with Th2-cells [10]. On one hand, ILC2 favor DC migration to the draining lymph nodes through the production of IL-13 and the initiation of Th2 responses [11•]. On the other hand, ILC2 contribute to the recruitment of type-2 inflammatory cells in the lungs by producing IL-5 and IL-13. Third, interestingly, IL-33 can activate Th2-cells in a TCR-independent manner, which amplifies inflammation [12,13,14•]. Besides mast cells, basophils and

**Figure 1**




Scheme of asthma induction. Allergens have often protease activity, which can directly damage epithelial cells releasing IL-33. These proteases bind to protease-activated receptor (PAR-2) at the surface of epithelial cells leading to the production of IL-25 and thymic stromal lymphopoïetin (TSLP). These mediators activate innate lymphoid cells (ILC)-2 and/or dendritic cells (DC). DCs that have picked up the allergen migrate to the lymph nodes where they instruct allergen-specific T-cells to become Th2-cells. IL-4 and IL-13 enable the commutation isotype switch to IgE by B-lymphocytes. Activated Th2-cells migrate to the tissue and together with innate inflammatory cells produce IL-4, IL-5, and IL-13 that are all deleterious in asthma. Mast cells and eosinophils (eo) can be activated through the binding of IgE on high affinity IgE receptors and crosslinking by the allergen. AHR: Airway hyper-reactivity.

eosinophils, NKT [15] and some macrophages can amplify allergic inflammation through the production of type 2 cytokines [16]. Of note, the disease evolves over time due to close interactions between the immune system and the lung tissue [7] promoting and sustaining inflammation and airway remodeling. Current treatments are mostly symptomatic even if the blockade of IL-4/IL-3 axis is currently proposed to stop Th2 inflammation [17,18]. Severe asthma is not associated with pure type-2 response. Thus a Th17 signature has been found in severe asthma [19], which could lead to propose Th2 and Th17-cells as therapeutic targets in some forms of asthma.

One interesting way to look for alternative therapies is to target ionic channels. First, ionic homeostasis is essential for the survival and functions of all the cells in basal and activated states. Second, this homeostasis is achieved through toolboxes containing different sets of ionic channels depending on the cell type. We will focus on some of the channels that have been tested at least in experimental asthma (Figure 3).

## Calcium channels as a target in asthma

Calcium ions ($Ca^{2+}$) act as a second messenger governing the cellular fate. Indeed, binding of $Ca^{2+}$ to EF hand-domains alters the properties of many proteins as structural proteins, enzymes (CaMK, PLCγ, and PKC), signaling molecules, molecules involved in contraction, exocytosis, membrane fusion, adhesion. Channels at the cell and ER plasma membrane let to increase intracellular $Ca^{2+}$ concentration ($[Ca^{2+}]_i$). We will describe some of them, the inhibition of which is beneficial in experimental asthma.

### STIM/ORAI channels, responsible for store-operated $Ca^{2+}$ entry in lymphocytes

In immune cells and especially lymphocytes, the most known calcium selective channels are the SOC ORAI1 calcium channels that are activated following ER $Ca^{2+}$ store depletion [20–23]. Indeed the T-cell receptor (TCR) recognition of its ligand (antigen peptide presented by self MHC molecules) induces the recruitment and phosphorylation of substrates (enzymes and adapters) by tyrosine kinases, which results in activation of