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Title:

Innate lymphoid cells in asthma: cannabinoids on the balance.

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The network of cells and soluble mediators implicated in the pathogenesis of asthma and allergic disorders is complex. Deciphering details of the crosstalk between its components is essential for the identification of novel drug targets and for advances in patient management and precision medicine (1, 2). There is increasing evidence that innate lymphoid cells (ILCs) contribute to allergic responses (3). ILCs represent subsets of lymphocytes that express distinct patterns of cytokines and, similar to T and B cells, arise from a common lymphoid progenitor (CLP) cell (4). Given that natural killer (NK) cells, the prototypical member of the ILC family (4), express Fc-receptors, their activity depends on the composition of the individual antibody repertoire (5, 6), but is also tightly balanced by activating and inhibitory receptors (7). NK cell inhibitory receptors are specific for MHC class I, whereas others recognize non-MHC protein or glycan ligands (7, 8). Furthermore, Massi et al. reported that endogenous cannabinoids inhibit NK cell activity by engagement of the G protein-coupled cannabinoid receptors CB1 and CB2 (9). In contrast to NK cells, which have been classified as group 1 ILC, group 2 innate lymphoid cells (ILC2) are characterized by the production of T helper 2 (T_H2) cell-associated cytokines (3), and increasing evidence demonstrates their contribution to allergic disorders, including asthma (reviewed in (4)). Recently, increased numbers of ILC2 cells in mucosal samples of patients with chronic rhinosinusitis (CRS) were shown to correlate with T_H2 cell frequency (10), supporting the notion that interactions between ILC2 cells and the adaptive immune system might take place during allergic inflammation (4). Does crosstalk also exist between ILC subsets such as NK cells and ILC2 in allergic inflammation and by what factors would it be influenced?

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In the current issue of *Allergy*, Ferrini et al. (11) provide evidence suggesting a role of NK cells in limiting ILC2 responses and subsequent allergic airway inflammation depending on NK cell regulation by CB2. Intranasal exposure to house dust mite (HDM) allergen led to reduced allergic airway inflammation in CB2^{-/-} mice, a finding that was also observed when WT animals were treated with the CB2-specific antagonist AM630. Interestingly, CB2^{-/-} mice displayed elevated numbers of NK cells in the lungs, which was inversely correlated with ILC2 frequency. Depletion of NK cells in CB2^{-/-} mice restored airway inflammation and was associated with increased ILC2 numbers in the lung. To confirm a regulatory effect of endocannabinoids on NK cell activation (9), in the present study NK cells were stimulated with anti-NK1.1 antibody obtaining a dose dependent inhibition of IFN- γ production by endocannabinoid 2-arachidonyl-glycerol (2-AG). Notably, adoptive transfer of CB2^{-/-}NK cells into WT hosts suppressed HDM-induced airway inflammation, suggesting that NK cells unrestrained by endogenous CB2 stimulation may act as gatekeepers to limit allergen responsiveness, eventually by mechanisms that include the regulation of allergy-promoting ILC2 cells.

Early studies in the seventies revealed a beneficial effect of inhaled or orally taken cannabinoids by dilating bronchial smooth muscles (12, 13). Since then, both anti- and pro-inflammatory effects of endocannabinoids have been reported, which has been attributed, in part, to bioactive metabolites and signalling by additional receptors, aside from CB1 and CB2, which are both expressed on human leukocytes (14). Several studies using mice lacking the CB2 receptor have shown exacerbated inflammation in different disease models (15). In contrast, Ferrini et al. (11) demonstrate in the HDM-induced asthma model using CB2^{-/-} mice that CB2 augments allergen responsiveness. Interestingly, an allergy promoting role of CB2 was also observed in an ear dermatitis model with CB2^{-/-} mice (16), and by the use of the CB2 receptor agonist JWH-133 in a OVA-induced asthma model with C57BL6 mice showing a direct effect of CB2 on eosinophil responses (17). This raises the question if

the immunomodulatory role of CB2 may depend on the type of immune response (e.g. allergic versus non-allergic). Further studies will be required to address this question or to exclude potential confounding variables, e.g. related to the disease model or mouse strain used (18, 19). In this regard, abnormalities in the development of several lymphocyte subsets have been reported in CB2^{-/-} mice (20).

The finding by Ferrini et al. (11) that NK cells may control ILC2 cells in allergic responses is intriguing. The exact mechanisms remain to be explored, but may include effects of NK cell-derived cytokines, such as IFN- γ (21), or other divergent strategies that NK cells employ for the control of immune cells (22). Given that NK cells are implicated in immune responses to viruses, the findings by Ferrini et al. (11) might indicate a potential mechanistic link between viral infection and T_H2-biased allergic airway disease (23). Furthermore, altered frequencies and functions of NK cells in asthma patients have previously been reported (24, 25). The study by Ferrini et al. (11) highlights the need to explore cellular networks including ILC cells in different individuals and phenotypes of allergic diseases to better understand these disorders at the clinical and mechanistic level (26).

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Figures

Figure 1 Putative role of NK cells as gatekeepers of the allergic party, which may involve the control of allergy-promoting ILC2 cells. The NK cell gatekeeper's attention is impaired by signalling through the cannabinoid receptor CB2 (left panel), and enhanced in absence of CB2, represented as broken cannabis pipe in the cartoon (right panel). Illustration by Aldona von Gunten.

