

## Review



# Role of Natural Killer Cells in Airway Inflammation

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## ABSTRACT

Natural killer (NK) cells have an immune regulatory function as well as cytotoxicity against tumor or infected cells. In the airway, although NK cells constitute a small proportion of the resident lymphocytes, they play an important role in the pathogenesis of chronic inflammatory airway diseases by modulating immune responses. NK cells can promote allergic airway inflammation by increasing the production of type 2 cytokines and inducing eosinophil migration. The increased activity of NK cells can develop or aggravate the destruction of lung parenchymal cells. On the other hand, decreased apoptotic activity of NK cells in eosinophils can serve as an aggravating factor for allergic airway inflammation. The increase in interferon- $\gamma$ -producing NK cells and the inhibition of type 2 immune response by NK cells can alleviate allergic airway inflammation. This review aims to define the roles of NK cells in chronic inflammatory diseases of lower and upper airways.

**Keywords:** Natural killer cells; inflammation; asthma; chronic obstructive pulmonary disease; allergic rhinitis; chronic rhinosinusitis

## INTRODUCTION

Natural killer (NK) cells are innate lymphocytes with natural cytotoxicity against infected and cancer cells located in non-lymphoid as well as lymphoid organs.<sup>1-5</sup> NK cells can be subdivided into phenotypically and functionally different populations on the basis of their relative expression of CD56 and CD16 surface markers. More differentiated CD56<sup>dim</sup>CD16<sup>+</sup> NK cells comprise up to 90% of the peripheral blood NK cells and contain high levels of perforin, granzymes and cytolytic granules. In contrast, immature CD56<sup>bright</sup>CD16<sup>dim/-</sup> NK cells are predominantly located in human peripheral tissues and are less cytotoxic, but produce large amount of cytokines such as interferon- $\gamma$  (IFN- $\gamma$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), granulocyte-macrophage colony-stimulating factor, interleukin (IL)-10 and IL-13 on stimulation. Furthermore, CD56<sup>dim</sup> NK cells are preferentially situated at acute inflammatory peripheral sites, while CD56<sup>bright</sup> NK cells migrate to chronic inflammatory sites.<sup>6,7</sup>

NK cells constitute about 10% of the resident lymphocytes in the lung, and a similar proportion in the blood. In the normal lung, cytotoxicity of NK cells is lacking unlike that in the blood; however, lung NK cell activity is augmented in the presence of IL-2.<sup>8</sup> A recent study

also reported that CD56<sup>dim</sup>CD16<sup>+</sup> NK cells constitute the majority of NK cells in human lungs and are less cytotoxic compared with CD56<sup>dim</sup> NK cells in peripheral blood. In addition, the number of lung NK cells expressing CD69 — a marker for tissue residency and activation — are few, and the expression of CD69 on NK cells was mainly confined to CD56<sup>bright</sup>CD16<sup>-</sup> NK cells and a small portion of CD56<sup>dim</sup>CD16<sup>+</sup> NK cells. These results therefore suggest that the majority of human lung NK cells are highly differentiated and hypofunctional CD69<sup>-</sup>CD56<sup>dim</sup> cells, which circulate between the blood and the lung.<sup>9</sup>

NK cells play an important role as regulatory cells in interactions with other immune cells through binding of multiple activating and inhibitory receptors on their surfaces and ligands on the target cells.<sup>1,2</sup> The airway is one of the main pathways for pathogen entry in acute infections and one of the common sites of chronic inflammatory disease. NK cells control chronic inflammation in airways and act rapidly to eliminate pathogens in acute respiratory infection.<sup>1,5</sup> Asthma and chronic obstructive pulmonary disease (COPD) in the lower airway as well as allergic rhinitis (AR) and chronic rhinosinusitis (CRS) in the upper airway exhibit both similar and different histological and immunological characteristics.<sup>10,11</sup> This review focuses on the role of NK cells in chronic inflammatory airway diseases.

### NK cells in lower airway inflammatory disease

#### *Asthma*

Asthma is a common chronic inflammatory disease in the lower airway and is characterized by recurrent symptoms such as wheezing, coughing, shortness of breath and/or chest tightness, reversible airflow obstruction and bronchospasm. It is caused not only by genetic factors but also by environmental factors such as air pollution and allergens.<sup>2</sup>

There is a debate about the role of NK cells in the pathogenesis of asthma. Some studies reported that the activity of NK cell was increased in asthmatic patients and that NK cells contributed to the promotion of allergic lung inflammation. Before allergen challenge, blood NK cell activity and IL-2 induced cytotoxicity in asthmatic patients were elevated compared with controls, whereas they were decreased after the allergen challenge.<sup>12</sup> NK-cell depletion before immunization by anti-NK 1.1 monoclonal antibody in an ovalbumin (OVA)-induced asthma mouse model showed significant decreases in pulmonary eosinophils, and IL-4 and IL-5 levels in bronchoalveolar lavage fluid. NK cells may play a critical role in determining the development of allergic eosinophilic airway disease.<sup>13</sup> IL-4<sup>+</sup>CD56<sup>+</sup> NK cells in peripheral blood mononuclear cells were increased in asthmatic patients and shifted toward IFN- $\gamma$ <sup>+</sup> NK cells after medical treatment.<sup>14</sup> In children with acute asthma, peripheral blood CD3<sup>-</sup>CD56<sup>+</sup> NK cells were increased, but ICAM-1 and L-selectin expression in blood NK cells was decreased.<sup>15</sup> NK cell-activating receptor NKG2D-deficient mice showed little pulmonary eosinophilia and few T helper type 2 (Th2) cells, which were restored by transfer of wild-type NK cells expressing granzyme B. These results suggested that NKG2D plays a role in the pathogenesis of house dust mite (HDM)-induced allergic airway inflammation.<sup>16</sup> NKG2D ligand major histocompatibility complex class I-related protein A (MICA) and UL16-binding protein-2 were increased in the serum of children with HDM allergy.<sup>17</sup> Activated CD69<sup>+</sup> NK cells in peripheral blood were negatively correlated with forced expiratory volume in 1 second (FEV1%), a parameter of the pulmonary function test, in asthmatic patients.<sup>18</sup>

In contrast, several other studies demonstrated that allergic eosinophilic airway inflammation can be inhibited by the enhancement of NK cell function. Stimulation of mouse airways using a combination of IL-2 and IL-8 suppressed airway hyperresponsiveness

and airway eosinophilic inflammation through up-regulation of IL-12 production and IL-12/STAT4-dependent cell signaling, followed by an increase in IFN- $\gamma$ <sup>+</sup> NK cells.<sup>19</sup> Eosinophil apoptosis induced by peripheral blood NK cells in severe asthmatic patients was significantly reduced despite increased expression of CD69 and NK cell-activating receptor NKG2D. Lipoxin A4 is known to inhibit eosinophil trafficking and tissue accumulation. In this study, its receptors were expressed on NK cells and lipoxin A4 enhanced NK cell-induced eosinophil apoptosis.<sup>20</sup> Prostaglandin I<sub>2</sub> (PGI<sub>2</sub>, prostacyclin) was known to augment immunosuppressive IL-10 production by Th2 cells.<sup>21</sup> In respect to the association between NK cells and type 2 innate lymphoid cells (ILC2) contributing to the allergic airway inflammation, the number of lung IFN- $\gamma$ -producing NK cells was increased in the prostaglandin I<sub>2</sub> receptor (IP)-deficient mice and was inversely correlated with ILC2 numbers. In addition, in IP-deficient mice exhibiting defective HDM-induced allergic airway inflammation, anti-NK-1.1 monoclonal antibody treatment restored allergic airway inflammation and elevated IL-13 producing ILC2. This study revealed that PGI<sub>2</sub> and its IP receptor regulate the number and activity of lung NK cells and that NK cells prevent allergic lung inflammation by limiting the number of ILC2s.<sup>22</sup> Cannabinoid receptors type 2 (CB2) are highly expressed on NK cells and its ligands are eicosanoids derived from arachidonic acid.<sup>23</sup> A similar phenomenon to that in IP-deficient mice was observed in CB2-deficient mice associated with the limitation of ILC2 activity by NK cells.<sup>24</sup> Natural cytotoxicity receptors (NCRs, including NKp30, NKp44, and NKp46) not only mediated target cell lysis but also regulated the homeostasis of immune response.<sup>25</sup> Allergic eosinophilic lung inflammation was more severe in NCR1-deficient mice than in NCR1<sup>+/+</sup> mice after OVA immunization, suggesting that NCR1 dampens the allergic reaction.<sup>26</sup> Thus, enhancing IFN- $\gamma$ -producing NK cells may be a therapeutic target for asthma.

In addition, Tubby *et al.*<sup>27</sup> reported that the number, receptor expression, mitogen-activated protein kinase (MAPK) signaling molecule expression, cytotoxic mediator expression and functional cytotoxicity of peripheral blood NK cells were not different between asthmatic patients with fixed airway obstruction and those without.

Thus, the exact role of NK cells in asthma pathogenesis is inconclusive and somewhat controversial. Further studies are need to better understand the role of NK cells in the pathogenesis of asthma.

#### COPD

COPD is a chronic inflammatory lung disease characterized by the limitation of airflow and its main symptoms include shortness of breath, chronic cough and sputum. The most common cause is cigarette smoking, which leads to chronic inflammation caused by innate and adaptive immune responses, followed by the emphysematous destruction of the parenchyma and the remodeling of the small-airway compartment.<sup>28</sup>

A number of studies examined the role of NK cells in the pathogenesis of COPD. The cytolytic activity of CD3<sup>+</sup>CD56<sup>+</sup> NK cells was reduced in the peripheral blood of smokers with COPD.<sup>29</sup> Lung NKp46<sup>+</sup> NK cells were not increase in number in mice exposed for 8 weeks to cigarette smoke (CS); however, lung leukocytes from CS-exposed mice treated with viral pathogen-associated molecular patterns (poly[I:C], ssRNA40 and ODN1826) exhibited an increase in IFN- $\gamma$ <sup>+</sup>NKp46<sup>+</sup> cells and a degranulation capacity compared with that of control mice. Therefore, this data demonstrated that NK cells may be important targets in controlling COPD exacerbation.<sup>30</sup> Similarly, although the expression of the activating receptors NK1.1, NKG2D and CD244 (2B4) were not changed in CS-exposed mice, NK cells from CS-exposed

mice were more cytotoxic to the NKG2D ligand RAET1 $\epsilon$ -expressing cells. Enhancement of IFN- $\gamma$  production after stimulation with IL-18 or L-12/IL-18 was not shown in CS-exposed NKG2D-deficient mice. Furthermore, airway damage and inflammation by influenza virus infection were reduced in CS-exposed NKG2D-deficient mice, and were restored by adoptive transfer of NKG2D<sup>+</sup> NK cells. These results indicate that NKG2D is a key mediator for NK cell hyperresponsiveness to long term exposure to CS and COPD aggravation following influenza virus infection.<sup>31</sup>

Likewise, Folli *et al.*<sup>32</sup> demonstrated NK cell hyperresponsiveness in COPD. The total number of NK cells or the expression of NK cell activating and inhibitory receptors in peripheral blood was not different between COPD patients and healthy subjects. However, NKG2D receptor expression was increased after stimulation with IL-2 and IL-12, and was decreased after budesonide and/or formoterol treatment. IL-2- and IL-12-induced IFN- $\gamma$  production was also decreased after treatment with budesonide, formoterol and the 2 in combination. Inhaled budesonide or formoterol treatment could reduce the activity of lung NK cells, even though they could not suppress peripheral blood NK cell activity.

The proportion, granzyme B expression and cytotoxicity of NK cells were increased, and the inhibitory receptor CD94 (Kp43) expression was decreased in bronchoalveolar lavage fluid from patients with COPD compared with healthy controls.<sup>33</sup> In concordance with bronchoalveolar lavage fluid NK cells, the dominant phenotype of lung NK cells was cytotoxic CD56<sup>+</sup>CD16<sup>+</sup>. Increased lung epithelial cells expressing major histocompatibility complex (MHC) class I chain-related protein A/MHC class I chain-related protein B (MICA/MICB) — the activating receptor NKG2D ligands — was correlated with the severity of COPD. Lung CD3<sup>+</sup>CD56<sup>+</sup> NK cells can kill lung parenchymal cells, and this natural toxicity of lung NK cells was greater in COPD patients than in control subjects with normal pulmonary function. These results suggested that the increased natural toxicity of NK cells to lung cells contributed to emphysema progression.<sup>34</sup>

Although peripheral blood CD3<sup>+</sup>CD56<sup>+</sup> NK cells were increased in COPD patients compared with healthy normal subjects, IFN- $\gamma$  secretion after stimulation of phorbol 12-myristate 13-acetate (PMA) and ionomycin was decreased in COPD patients. Inhibitory receptor CD158a<sup>+</sup> and CD158b<sup>+</sup> NK cells were increased in COPD patients, and were negatively correlated with pulmonary function. Thus, increased numbers of NK cells expressing inhibitory receptors may be involved in the pathogenesis of COPD.<sup>35</sup> Thus, most studies demonstrated that the activation of the receptor NKG2D and the increased cytotoxicity of NK cells are responsible for the chronic inflammation and destruction of lung parenchymal cells in COPD.

### NK cells in upper airway inflammatory disease

#### AR

AR is a symptomatic disorder of the nose characterized by nasal congestion, watery rhinorrhea, sneezing and nasal itching induced after allergen exposure by an immunoglobulin E-mediated inflammation of the nasal mucosa. Patients with AR are commonly associated with allergic conjunctivitis and asthma.<sup>36</sup> The pathogenesis and pathophysiology of AR are closely related with those of allergic asthma.<sup>10,11</sup> As with asthma, the role of NK cells in the pathogenesis of AR is controversial.

Activated CD56<sup>+</sup>CD69<sup>+</sup> NK cells were increased in peripheral blood from AR patients.<sup>37</sup> As with asthma, IL-4<sup>+</sup>CD56<sup>+</sup> NK cells in peripheral blood mononuclear cells and IL-13 secretion

by NK cells were increased in AR patients. The expression of CD178 (Fas ligand) involving apoptosis and cytotoxic activity were higher in AR patients than in healthy controls.<sup>38</sup> Moreover, NK cell supernatants from AR patients induced eosinophil chemotaxis, which was augmented by IL-15 treatment and blocked by neutralizing anti-IL-8 antibody. The IL-8 production of NK cells was increased by IL-15 treatment and decreased by vitamin D<sub>3</sub>. Therefore, crosstalk between NK cells and eosinophils in AR is mediated by the IL-15/IL-8 axis modulated by vitamin D<sub>3</sub>.<sup>39</sup>

On the contrary, CD56<sup>bright</sup>CD16<sup>+/-</sup> NK cells in peripheral blood were significantly decreased in patients with AR compared with healthy controls. IFN- $\gamma$  production of NK cells in response to dendritic cells was also decreased in AR patients. NK cell-induced dendritic cell maturation and the NK cell capability to kill immature dendritic cells were reduced in AR patients. Therefore, the regulatory function of NK cells in maintaining Th1 response may be impaired in AR.<sup>40</sup> In AR patients, diesel exhaust exposure increased the levels of eosinophilic cationic protein in nasal lavage fluid and decreased the cytotoxic activity of NK cells on eosinophils in peripheral blood, indicating that diesel exhaust particles may exacerbate AR by reducing the ability of NK cells to clear eosinophils.<sup>41</sup>

#### CRS

CRS is a chronic inflammatory disease of the nose and the paranasal sinuses characterized by nasal obstruction, nasal discharge, facial pressure, and/or reduction or loss of smell lasting at least 12 weeks. CRS is caused by multiple factors and is frequently associated with asthma and allergy.<sup>42</sup>

The number of NKp46<sup>+</sup> NK cells in the nasal subepithelial layer was increased in patients with allergic CRS (ACRS) without asthma compared with healthy controls and ACRS patients with asthma. Chemokine receptor CX3CR1 on NK cells and CXCL1 and eotaxin-3/CCL26-induced NK cell migration were increased after nasal challenge with allergens in AR patients. NK cell infiltration in allergic nasal tissue may be mediated by CX3CL1- and CCL26-inducing NK cell chemotaxis via CX3CR1.<sup>43</sup>

We first reported impairment of degranulation ability and IFN- $\gamma$ /TNF- $\alpha$  production in peripheral blood NK cell from patients with CRS. These defects were obvious in the treatment-recalcitrant group and patients with concomitant asthma or peripheral blood eosinophilia. Therefore, NK cell dysfunction may contribute to CRS pathogenesis in respect to eosinophilic inflammation.<sup>3</sup> Furthermore, we clarified that NK cell dysfunction was involved in the exacerbation of eosinophilic inflammation. NK cell depletion before immunization increased eosinophilic infiltration, IL-5 secretion and peripheral blood eosinophilia in an OVA-induced allergic rhinosinusitis mouse model.<sup>4</sup>

Peripheral blood NK cell-mediated eosinophil apoptosis was decreased in eosinophilic CRS, and sinus tissue NKp46<sup>+</sup> NK cells counts were inversely correlated with tissue eosinophil counts. NK cell depletion in an eosinophilic CRS mouse model resulted an aggravation of eosinophilic sinonasal inflammation and a decrease in apoptotic eosinophils in sinonasal tissue. Prostaglandin D<sub>2</sub> (PGD<sub>2</sub>)—which has been reported to suppress NK cell effector functions<sup>44</sup>—and its metabolites were elevated in CRS patients and attenuated NK cell-mediated eosinophil apoptosis as well as degranulation activity and IFN- $\gamma$  production of NK cells. The expression of the activating receptors CD16, NKG2C, NKG2D or 2B4, the expression of which did not differ between CRS patients and healthy controls,<sup>3</sup> was also

**Table.** The relationship between NK cell function and its impact on chronic airway inflammatory diseases

Type of inflammatory disease	NK cell phenotype	Impact of NK cells on the pathogenesis of diseases	References
Asthma	↑IL-4 <sup>+</sup> NK cells	Aggravation	Wei <i>et al.</i> <sup>14</sup>
	↑NKG2D <sup>+</sup> NK cells	Aggravation	Farhadi <i>et al.</i> <sup>16</sup>
	↑CD69 <sup>+</sup> NK cells	Aggravation	Ishimori <i>et al.</i> <sup>18</sup>
	↑IFN-γ <sup>+</sup> NK cells	Suppression	Matsubara <i>et al.</i> <sup>19</sup>
			Simons <i>et al.</i> <sup>22</sup>
			Ferrini <i>et al.</i> <sup>24</sup>
COPD	↑NCR1 <sup>+</sup> NK cells	Suppression	Elhaik Goldman <i>et al.</i> <sup>26</sup>
	↑IFN-γ <sup>+</sup> NKp46 <sup>+</sup> NK cells	Aggravation	Motz <i>et al.</i> <sup>30</sup>
	↑NKG2D <sup>+</sup> NK cells	Aggravation	Wortham <i>et al.</i> <sup>31</sup>
			Folli <i>et al.</i> <sup>32</sup>
	↑CD56 <sup>+</sup> CD16 <sup>+</sup> NK cells	Aggravation	Hodge <i>et al.</i> <sup>33</sup>
AR	↑IL-4 <sup>+</sup> CD56 <sup>+</sup> NK cells	Aggravation	Mesdaghi <i>et al.</i> <sup>38</sup>
	↓CD56 <sup>bright</sup> CD16 <sup>+</sup> NK cells	Aggravation	Scordamaglia <i>et al.</i> <sup>40</sup>
CRS	↑NKp46 <sup>+</sup> NK cells	Aggravation	El-Shazly <i>et al.</i> <sup>43</sup>
	↓NKp46 <sup>+</sup> NK cells	Aggravation	Kim <i>et al.</i> <sup>4,5</sup>
	↓IFN-γ <sup>+</sup> , CD107a <sup>+</sup> NK cells	Aggravation	Kim <i>et al.</i> <sup>3,5</sup>

NK, natural killer; IL, interleukin; IFN, interferon; NCR, natural cytotoxicity receptor; COPD, chronic obstructive pulmonary disease; AR, allergic rhinitis; CRS, chronic rhinosinusitis.

not affected by PGD<sub>2</sub> treatment. Thus, eosinophilic inflammation in CRS is closely related to PGD<sub>2</sub> dysregulation and the subsequent impairment of NK cell-mediated eosinophil apoptosis. The suppression of PGD<sub>2</sub>, followed by the recovery of NK cell activity, may be potential therapeutic targets in eosinophilic CRS.<sup>5</sup>

## CONCLUSIONS

NK cells enhance or inhibit immune responses in the airway. In asthma and AR, increased type 2 cytokine-producing NK cells can promote allergic inflammation, while enhancement of NK cells can inhibit allergic inflammation by increasing eosinophil apoptosis or restricting type 2 immune responses. Increased cytotoxicity of NK cells contributes to the destruction of lung parenchymal cells in COPD. Eosinophilic inflammation of CRS patients is attributed to the decreased degranulation ability, IFN-γ production and ability of NK cells to induce eosinophil apoptosis. Thus, NK cells play various roles in the chronic inflammatory airway (Table). In order to utilize NK cells as a therapeutic target, it is necessary to establish a therapeutic strategy for controlling their functions in consideration of the basic functions of NK cells in each disease.

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