Nature Reviews Immunology | Published online 26 May 2017; doi:10.1038/nri.2017.60

ASTHMA AND ALLERGY

The NET effect of respiratory viruses

> inhibitors of NETosis could be useful for treating virus-induced asthma exacerbations

A new study in *Nature Medicine* provides fresh insight into why respiratory viral infections exacerbate asthma. Toussaint *et al.* show that rhinovirus infections (which cause the common cold) drive the release of neutrophil extracellular traps (NETs) that can intensify type 2 immune responses in the allergic airways.

Respiratory viral infections are typically associated with type 1 immune responses, and it has been unclear why they lead to more severe asthma, as this disease is associated with type 2 immune responses. As respiratory viral infections promote airway neutrophilia, Toussaint *et al.* hypothesized that the release of NETs containing host DNA may exacerbate airway inflammation in asthmatics. To explore this idea, individuals with mild to moderate atopic asthma and healthy controls were intranasally infected with rhinovirus 16 (RV-16), an RNA virus with no DNA intermediates. They analysed nasal lavage samples and found that levels of double-stranded DNA (dsDNA) were increased in the samples from both healthy individuals and asthmatics at day 2 following RV-16 challenge, but were even higher in the samples from the asthmatics. The levels of dsDNA in the samples from healthy individuals had returned to baseline levels by day 3, but individuals with asthma still showed elevated levels of dsDNA at day 10 after RV-16 infection. Notably, increased levels of dsDNA in nasal lavages positively correlated with increased levels of type 2 cytokines, and also correlated with cold-symptom severity and the severity of asthma exacerbation following RV-16 infection.

The authors next used a mouse model of house dust mite (HDM) allergen-induced asthma to explore the mechanisms involved. They found that HDM-sensitized mice that were challenged with live rhinovirus 1b (RV-1b) showed exacerbated allergic airway inflammation compared with HDM-sensitized mice challenged with inactivated RV-1b. Allergic mice infected with RV-1b also had higher levels of dsDNA in bronchoalveolar lavage fluid (BALF) compared with RV-1b-infected naive mice or allergic mice challenged with inactivated RV-1b. Treatment with DNase substantially reduced type 2 immune responses in the airways of RV-1b-infected allergic mice, and this was associated with lower production of chemokines and reduced recruitment of monocyte-derived dendritic cells to the airways and mediastinal lymph nodes.

Finally, the authors examined whether the release of dsDNA during rhinovirus infection is due to NET release by neutrophils in the airways. The NET-associated protein neutrophil elastase was only detected in nasal lavages from individuals with asthma and not in those from healthy controls following RV-16 infection. Similar observations were made in mice, and immunostaining for NET-associated proteins showed that NETs were abundant in the lungs of both allergic and non-allergic RV-1b-infected mice, but were absent in RV-1b-infected mice that had been treated with antibodies to block neutrophil recruitment. When RV-1b-infected allergic mice were treated with a specific inhibitor of NETosis, they had similar viral loads and neutrophil numbers in their BALF compared with vehicle-treated control animals, but they showed a decrease in allergic airway inflammation.

Although it remains to be determined exactly how rhinovirus infections drive NETosis, the authors suggest that inhibitors of NETosis could be useful for treating virus-induced asthma exacerbations.

Yvonne Bordon

ORIGINAL ARTICLE Toussaint, M. *et al.* Host DNA released by NETosis promotes rhinovirus-induced type-2 allergic asthma exacerbation. *Nat. Med.* http://dx.doi.org/10.1038/nm.4332 (2017)