Do our immune cells shape asthma severity?

Tara Sutherland

Asthma is one of the world's most common chronic lung diseases. It affects more than 5.4 million people in the UK alone. Here, immunologist Tara Sutherland explains how inflammation can impact asthma severity, and how we can use this information to re-think treatment options for asthmatic patients

AQA: 3.2.4 Cell recognition and the immune system

Edexcel A: 6 Immunity, infection and forensics

Edexcel B: 6.7 Response to infection

OCR A: 4.1.1 Communicable diseases, disease prevention and the immune system

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Eosinophils

Asthma is not just a wheezy chest and cough that can be treated with a puff on an inhaler. Three people in the UK die from asthma-related complications every day. Asthma is caused by a combination of genetic and environmental influences that lead to an inappropriate chronic activation of the airway immune system. The type of immune response, associated inflammation and the factors that trigger this reaction vary greatly between patients. Unravelling these complex immune responses will aid development of new asthmatic drugs.

Types of inflammation in asthma

Asthma is commonly triggered when a pre-**sensitised** person encounters an **allergen** such as dust mite droppings (see Figure 1), moulds or pet dander (skin flakes). The immune reaction that follows sets off a cascade of inflammation, leading to airway contraction (see Figure 2), difficulty breathing and wheeziness. This classic allergic immune response is characterised by **type 2 inflammation** (see Box 1). Asthmatics with type 2 allergic disease often respond well to anti-inflammatory drugs, including glucocorticoid steroids — the mainstay for asthma treatment — alongside the **bronchodilator** salbutamol. Drugs that neutralise type 2 **cytokines** or IgE antibodies (see Box 1) can be used for asthma that is poorly controlled by traditional treatments.

Given several treatment options, why do some people still experience profound asthma symptoms or even die from disease complications? The answer is that not all asthmatics have allergic disease. While doctors and researchers have always appreciated that asthmatics have varying disease symptoms and treatment responses, it was only recently that the implications of this surfaced. Current research is now enabling doctors to classify asthmatics into different groups according to their disease type, severity and likelihood of responding to specific treatments.

Neutrophils: good or bad for asthmatics?

Neutrophils are cells that form the body's first line of defence against infections. However, some patients with severe asthma have increased numbers of neutrophils in their lungs. Neutrophils release **cytotoxic** molecules that kill invading pathogens but if neutrophils are not controlled, or are triggered inappropriately, these toxic substances can harm our own cells. Thus, it seems logical that the presence of neutrophils could be a cause of increased tissue changes seen in severe asthmatics.

While neutrophils normally live for 1–2 days, glucocorticoid steroids can increase their lifespan. Furthermore, unlike type 2 cytokines, levels of interleukin (IL)-17, a neutrophil-attracting cytokine, are not reduced by steroid treatment. So neutrophils may be the dominant inflammatory cells in severe asthmatics purely because they are resistant to steroids. This leaves us questioning whether neutrophils really are the problem, or purely reflect poor treatment choice.

So why do some asthmatics have neutrophil inflammation? We all share our bodies with an ecosystem of microorganisms that help us digest food and toxins, make vitamins and enable our immune system to keep us healthy. This **microbiome** is present in the gut and skin, as well as the lungs (see Biological Sciences Review, Vol. 31, No. 1, pp. 2–6). The composition of the lung microbiome differs in

Figure 1 Coloured scanning electron micrograph of a dust mite. Millions of dust mites inhabit our homes, feeding on shed skin cells. They mainly live in carpets and furniture. They are usually harmless but enzymes in their droppings may cause allergic reactions in susceptible people (×400)

asthmatics and non-asthmatics, and the differences can be associated with neutrophilic inflammation. So there could be a relationship between our microbiome and the development, degree or type of airway inflammation in asthmatics.

As neutrophils are key immune defence cells, it is not surprising that airway neutrophils can indicate the presence of viral or fungal infections in asthmatics. This suggests that increased neutrophil numbers in severe asthmatics reflect an unbalanced microorganism load, whether it be infections with viruses or fungi or changes to our microbiome. The problem is that research still does not tell us whether neutrophils do contribute to asthma pathology. However, if we consider the actions of neutrophils, we can start to see how neutrophil inflammation might make asthma pathology worse.

Neutrophils can **phagocytose** particles or microorganisms, releasing their stored proteins and enzymes to attack a microorganism. They can also release a DNA web, called a **neutrophil extracellular trap** (NET) (see Box 2) that immobilises microorganisms. These neutrophil defence mechanisms are efficient pathogen killers,

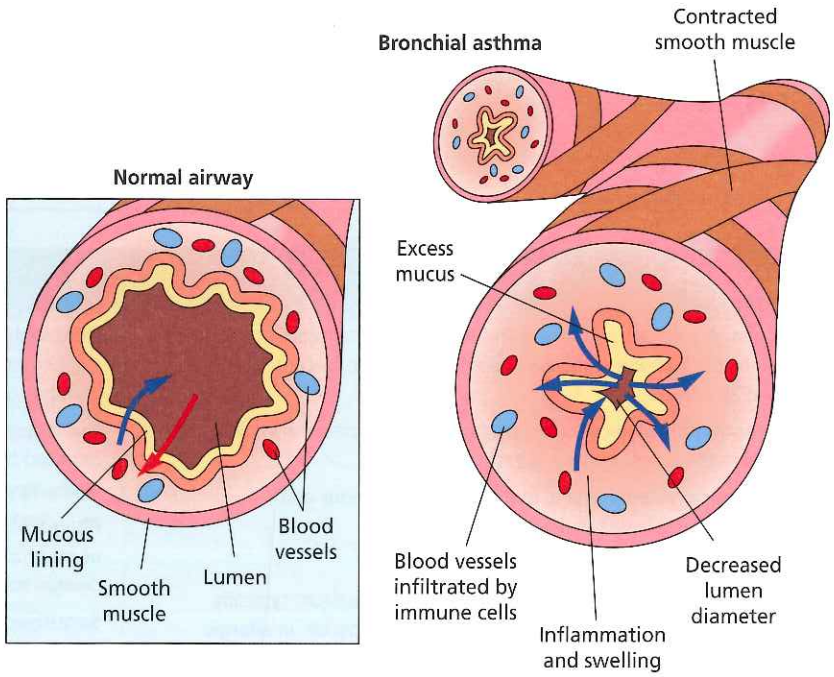


Figure 2 A diagram of the bronchi in an asthmatic versus a healthy individual. Image shows broncho-constriction, airway inflammation and excessive mucus production, all of which lead to difficulty breathing and wheeziness in asthma

Box 1 Allergic asthma and type 2 inflammation

The body's immune system is our main protective defence mechanism against pathogens. Immune responses that generate type 1 cytokines control infections from intracellular pathogens (bacteria and viruses), while type 2 cytokine responses control infection by extracellular parasites. However, in some people these protective type 2 responses can become activated by triggers, such as allergens, that are normally harmless. This inappropriate inflammatory immune response, if not controlled, can lead to chronic inflammation, as seen in asthma.

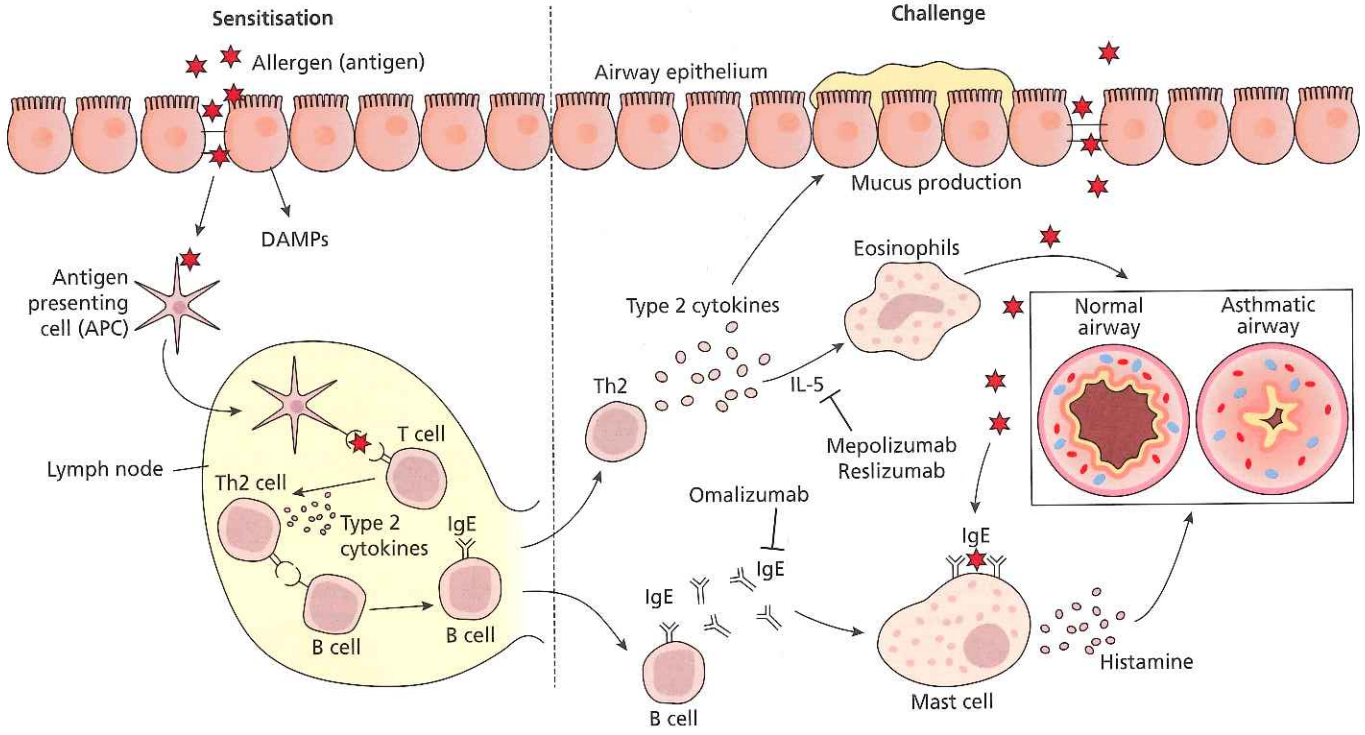
The immune response in allergic asthma occurs after initial sensitisation to an allergen. Here, allergens often have enzymatic activity allowing them to break through the airway epithelium. Damaged epithelial cells then secrete danger signal molecules (DAMPs), alerting and preparing immune cells for an ensuing allergen attack. Antigen-presenting cells take up and process allergen before migrating to nearby lymph nodes where antigen is presented to naive T cells. These T cells become primed and activated, and turn into Th2 cells, secreting type 2 cytokines and stimulating B cells to produce IgE antibodies — immunoglobulins strongly associated with allergy. Once sensitised, re-exposure to the allergen initiates a cascade of events:

1 IgE binds high-affinity IgE receptors on mast cells, and when an individual is re-exposed to antigen, this antigen is recognised by the antigen-specific IgE and causes mast cell activation and release of mediators like histamine.

2 Th2 cells migrate into the lungs.

3 Type 2 cytokines recruit numerous cells, like eosinophils, from the bloodstream.

These inflammatory events all contribute to narrowing of the airway.



Terms explained

Allergen A substance (antigen) that is normally harmless but triggers an abnormal immune response in some individuals because it is treated as a threat.

Bronchodilator Medication that relaxes the muscles and widens the bronchi in the lungs, making it easier to breathe.

Cytokines Secreted proteins that alter the behaviour and communication of surrounding cells.

Cytotoxic An agent that is toxic to living cells.

Eosinophils A white blood cell with a bi-lobed nucleus; typically found in high numbers during inflammation that occurs in allergic disorders and parasitic infections.

Microbiome Microorganisms that are unique to each individual; important for maintaining normal health but when unbalanced can lead to a dysregulated immune response.

Neutrophils Immune cells containing characteristic granules and a segmented distinct nucleus; often the first responders of the innate immune system following infection or injury.

Neutrophil extracellular trap (NET) Granule proteins bound to DNA released from an activated neutrophil to form a web-like mesh that binds, traps and kills microorganisms.

Phagocytosis The process by which a cell, classically a macrophage or neutrophil, engulfs and internalises a particle or organism within a compartment called a phagosome.

Sensitised Production of antibodies by the immune system in response to a substance it considers foreign, such as an allergen.

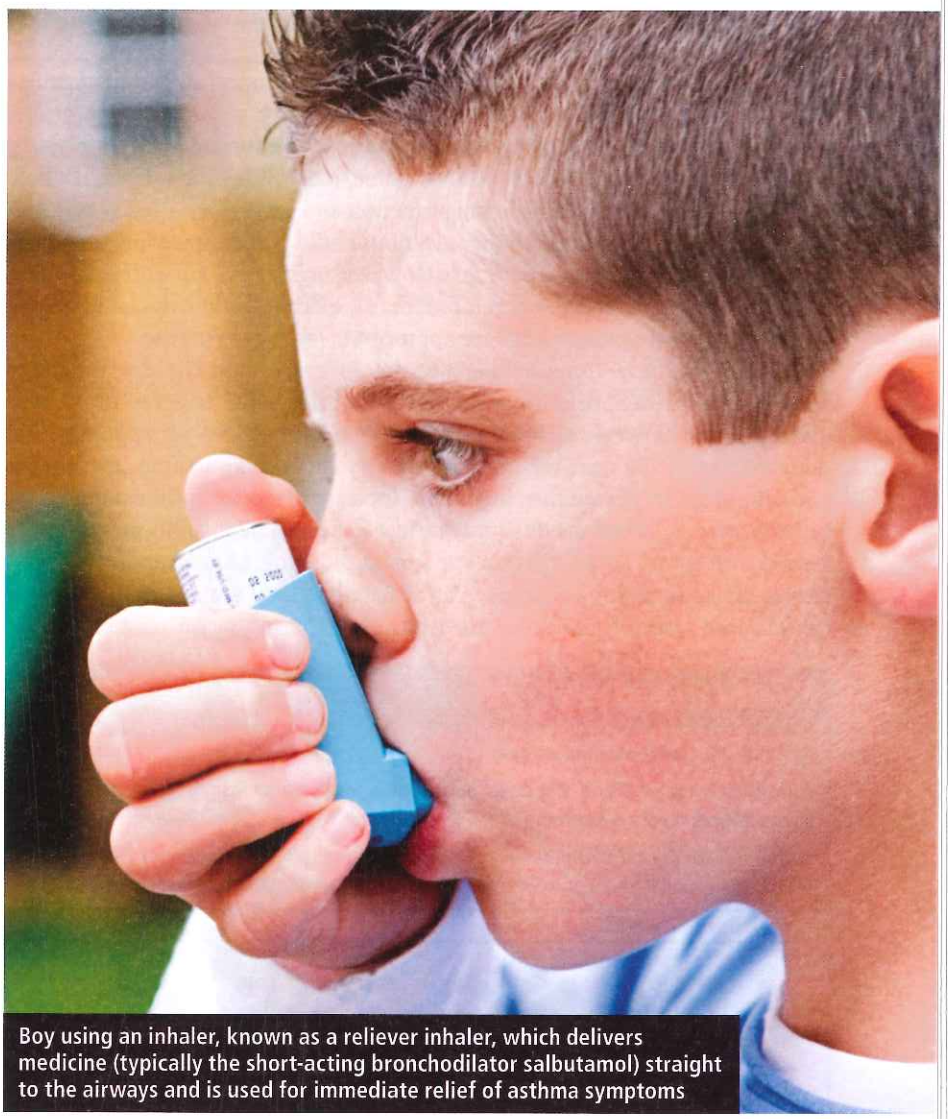
Type 2 inflammation Response typically induced by parasitic infection or allergic responses; characterised by the action of type 2 cytokines (e.g. IL-4, IL-5, IL-13) and accumulation of eosinophils.

but if provoked inappropriately they can cause physical damage. For instance, in a mouse model of asthma, NET release triggered by viral infection stimulates type 2 cytokine production, leading to increased **eosinophil** inflammation. Therefore, neutrophil activation may contribute to asthma severity by enhancing inflammation.

New treatments for asthma

If neutrophils really are pathogenic in asthmatics, then might treatments directed at neutrophils be beneficial? Considering the success of type 2 cytokine inhibitors for eosinophilic asthma (see Box 1), it would be reasonable to assume a similar approach targeting IL-17 could be beneficial for neutrophilic asthma. Several clinical trials have been performed using drugs that neutralise IL-17 but the results were disappointing. Patients with poorly controlled asthma who were given an IL-17 inhibitor showed no obvious improvement in lung function or symptoms.

Did researchers get it all wrong and IL-17/neutrophils are merely a symptom and not the cause of severe asthma? While it is possible that IL-17 is not critical in severe asthma, we have to consider the types of asthmatic patients that were selected for these clinical trials. As alluded to earlier, asthma patients do not all have a similar disease. Asthma comes in different shapes and sizes. Therefore, grouping patients together on the basis of poorly controlled severe disease will not necessarily select patients with neutrophilic/IL-17 inflammation. A better approach might involve pre-screening patients for IL-17 levels to inform which individuals are more likely to respond to

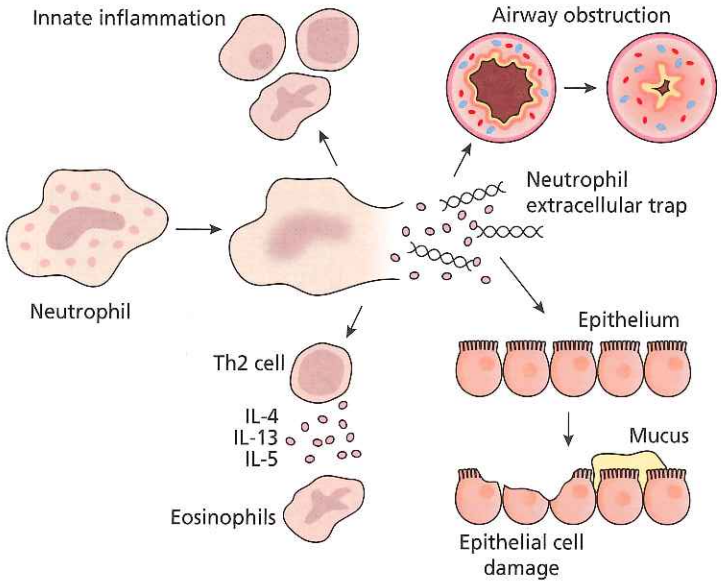


Boy using an inhaler, known as a reliever inhaler, which delivers medicine (typically the short-acting bronchodilator salbutamol) straight to the airways and is used for immediate relief of asthma symptoms

Box 2 Neutrophil extracellular traps

Neutrophils are one of the most important cells that fend off unwanted pathogen attacks. However, neutrophils can cause damage to host tissue. Neutrophil extracellular traps (NETs) were first described about 15 years ago as a defence mechanism against bacterial pathogens. On activation, neutrophils can spew out a web-like meshwork of chromatin (DNA and histones) that is decorated with neutrophil granule proteins and antimicrobial enzymes. It is easy to envisage these web-like structures trapping and killing pathogens in their wake. However, considering the toxicity of neutrophil proteins/enzymes, it is not difficult to imagine that NETs can also be damaging. NETs can damage cell–cell junctions, increase mucus production, increase inflammation, and obstruct the airways, all characteristic features of asthma. NETs have been found in the airways of asthmatics.

Experiments using neutrophils from severe asthmatic patients suggest that NETs degrade epithelial cell junctions that function to control passage of molecules and ions through the space between cells. Changes to cell–cell junctions could contribute to the severity of asthmatic disease because a breach in the epithelial layer allows allergens free access to the lungs.



IL-17 inhibitors. Only then are we likely to understand whether IL-17 inhibition could benefit some asthmatics.

A different treatment approach to deal with neutrophil inflammation has been tested in other clinical trials and results have shown more promise. Considering that severe neutrophilic asthma can be associated with infections, anti-bacterial and anti-viral products called macrolides have been trialled. Short-term treatments improved lung function and patient-reported symptoms, suggesting that treating underlying infections could reduce neutrophil numbers and in turn reduce disease severity. However, in the age of worrying about microbial resistance and the development of superbugs, some researchers have questioned whether macrolides are appropriate for long-term use.

Overall, we have come a long way in understanding the disease called asthma. As airway inflammation and environmental triggers that cause disease differ between asthmatics, the one treatment fits all approach was doomed to fail. So next we need to identify individual asthma phenotypes and take steps to personalise medicine. Increases in neutrophil numbers can be indicative of infections or simply reflect increased neutrophil survival after steroid treatments, so we still don't understand the role of neutrophils in severe steroid-resistant asthma. Irrespective of whether they are a symptom or the cause, more research is needed to determine whether targeting neutrophils, or neutrophil-associated cytokines, could prove beneficial in some asthmatic patients.

Further reading

Asthma UK: **www.asthma.org.uk**

Atlas of Science — Using 'Big Data' approaches to gain new insights into asthma: **https://tinyurl.com/ydephvng**

U-Biopred (**U**nbiased **BIO**markers in **PRED**iction of respiratory disease outcomes): **www.europeanlung.org/projects-and-research/projects/u-biopred/home**

Dr Tara Sutherland is an immunology research fellow in the Lydia Becker Institute for Inflammation and Infection Research and the Manchester Collaborative Centre for Inflammation Research (MCCIR), University of Manchester. Her research focuses on how immune responses in the lung can influence structural pathology changes to the tissue. She also teaches undergraduate and postgraduate students about immune responses in asthma.

Key points

- Asthma is a chronic inflammatory disease of the airways that can be triggered by many different things, including allergens.
- Asthmatic patients can have different types of inflammatory cells in their airways and these differences can help define the type and severity of asthma.
- Neutrophils are a type of inflammatory cell that can accumulate in the airways of some asthmatics and can be a sign of more severe disease.
- Controlling inflammation in some asthmatics may be improved if we can specifically target the inflammatory cells that are most abundant in each individual patient.