Protecting the lungs against 'collateral damage' from the immune system

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A study published today in the journal *Science* shows how our bodies try to minimise potential 'collateral damage' caused by our immune system when fighting infection. The research may also provide new clues to why cigarette smoke is a significant risk factor for developing diseases of the lung such as chronic bronchitis and emphysema.

When bacteria or viruses enter the body, our immune system fights back to neutralise any danger. One of the key 'soldiers' working for the immune system is a particular type of cell known as a neutrophil, which releases toxic enzymes to kill the invading organism. But these enzymes can cause collateral damage to surrounding tissue, and so the neutrophils need to act swiftly and leave the site of infection as quickly as possible.

"Neutrophils are powerful at fighting infection, but if left unchecked, they can cause damage to our own bodies," explains Dr Robert Snelgrove, a Sir Henry Wellcome Postdoctoral Fellow at Imperial College London, who carried out the study together with colleagues from the University of Alabama at Birmingham, USA. "We know that their persistence contributes to the development and severity of many chronic lung diseases such as chronic obstructive pulmonary disease and cystic fibrosis."

The enzymes released by neutrophils can cause particular damage in the lung, where they can attack the collagen which makes up the lung's architecture, selectively cutting out a molecular fragment known as PGP. This fragment in turn recruits more neutrophils, potentially leading to a

vicious circle of damage.

However, in research published today and part-funded by the Wellcome Trust, Dr Snelgrove and colleagues show how another enzyme released by the lungs - LTA4H - degrades PGP, breaking the cycle and preventing damage.

In a second experiment, the researchers also showed that chemicals found in cigarette smoke can have a negative effect on this process, modifying PGP in a way that increases its ability to recruit more neutrophils and protecting it from degradation, and inhibiting the performance of LTA4H.

Patients with diseases such as chronic bronchitis and emphysema, which are collectively known as chronic obstructive pulmonary disease (COPD), tend to have persistent neutrophils in the lungs

"We have known for some time now that there is a link between smoking and COPD," says Dr Snelgrove. "Here we have shown that cigarette smoke can severely limit the effectiveness of an enzyme which contributes to the clearance of these rogue immune cells. This may be a contributing factor to damage to the lungs which affects a person's ability to breathe easily."

There are an estimated three million people in the UK living with diseases such as chronic bronchitis and emphysema, which are collectively known as chronic obstructive pulmonary disease (COPD). This condition is caused by damage to the lungs, most commonly as a result of smoking, and leads to an inability to breathe properly.

The researchers believe that the research may have implications for the development of new drugs aimed at treating acute and inflammatory diseases. As well as working to reduce inflammation, LTA4H more

commonly works to promote inflammation. However, drugs aimed at inhibiting the pro-inflammatory activity of LTA4H could have repercussions for preventing degradation of PGP, causing potential lung damage, they caution.

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