Asthma is a common, long-term lung condition that affects over 250 million children and adults around the world. The disease is often triggered by aberrant immune responses to respiratory infections and inhaled allergens, such as dust, pollen, and animal fur/feathers. The condition is caused by inflammation and narrowing of the small airways in the lungs, which leads to the characteristic symptoms of asthma, including coughing, wheezing, shortness of breath, and chest tightness. Most people with asthma can manage the condition with inhaled medications. However, up to 15% of people with asthma may have severe asthma, defined as uncontrollable asthma; symptoms and poor response to treatment lead to increased numbers of asthma exacerbations and hospitalisations. As a result, severe asthma accounts for a disproportionate burden on healthcare costs.

Learning more about the molecular mechanisms underlying severe asthma may help scientists to develop novel therapies to treat the condition. This would improve quality of life for people with severe asthma and make treatment more cost- and resource effective.

MicroRNAs and Gene Expression

While a graduate student with Professor Carole Ober at the University of Chicago, explored changes in airway cells from people with and without asthma. They found that changes to small molecules called microRNAs modulate inflammation and immune responses that may lead to severe asthma.

MicroRNAs, or miRNAs, are small molecules that play important roles in regulating gene expression. The term ‘gene expression’ refers to the process by which information from a gene is used to synthesise molecules that orchestrate biological processes. Altering gene expression can change the way a cell works. For example, if a gene expression is upregulated, then the proteins or other molecules encoded by this gene may be synthesised in higher amounts. While many genes are referred to as ‘coding’ because they produce proteins with various functions, miRNAs are non-coding in that they do not produce proteins but rather have key regulatory functions – they bind to the RNA transcripts of other genes and downregulate their expression. At least 60% of genes in the human genome are thought to be regulated by miRNAs.

The researchers explain that differences in miRNA levels have been observed in cells from the airways of people with and without asthma. For example, previous studies linked miRNA-mediated reductions in gene expression to the pathogenesis of asthma. This suggested that miRNA molecules may play a significant role in regulating asthma and asthma symptoms.

MicroRNAs can be altered by an editing process called ‘adenosine deaminase acting on RNA’ (ADAR)-mediated editing. This is the most widespread RNA-editing process in humans, with over 50,000 suggested edited sites identified in human cells. This editing results in changes in the sequence of the miRNA and the ability of the miRNA to target and regulate gene expression. The unedited version of the miRNA does not downregulate the genes, hence the increased expression of inflammation-promoting genes in the asthma cases and the dampening of expression of those genes in non-asthmatic controls.

Learning more about the molecular mechanisms underlying severe asthma may help scientists to develop novel therapies to treat the condition.
Behind the Research

Dr Kevin M Magnaye
Professor Carole Ober

Research Objectives

The researchers performed the first genome-wide study of ADAR-mediated editing of miRNAs in airways cells from asthma patients.

Personal Response

What are you planning to study next?

In this study, we interrogated A-to-I edited sites in miRNAs that are found in only a very small fraction of the human genome. Over 50,000 A-to-I edited sites are known across the genome, most of which are found outside of the human genome. Over 50,000 A-to-I edited sites are known across the genome, most of which are found outside of miRNAs. Our next step is to identify A-to-I edited sites in other regions of the genome in airway cells and test whether these sites relate to asthma and asthma-related traits.

Could you explain the differences between RNA editing and the gene editing processes we so often hear mentioned in the news?

The most common gene editing processes involve CRISPR-Cas9 technologies that induce targeted changes in DNA. These are powerful techniques that can edit mutations known to cause disease in humans. Similarly, RNA editing involves single-base changes in RNA. Here, we identified a naturally occurring RNA (A-to-I) edited site that was associated with asthma severity. Editing technologies that target RNA are currently being developed and may also be used to treat human diseases in the near future, such as the RNA-edited site observed in our study.

Dr Magnaye and Professor Ober's research might lead to new treatment options for people with severe asthma.

LESS SEVERE ASTHMA

No editing of target site

SOC51

LES SEVERE ASTHMA

Editing of target site

SOC51

MORE SEVERE ASTHMA

More editing means less binding and downregulation of a target gene, SOCS1, which is then overexpressed in the airway cells from these individuals, presumably promoting symptoms in poorly-controlled asthma.

CONCLUSION

The research team point out that increased editing in this specific miRNA has also been observed in tumour cells of patients with lung cancer, compared to healthy tissue from the same individuals. Therefore, editing at this site appears to be either disease-promoting, in the case of lung cancer, or disease-protective, as with asthma. This suggests that there may be other unknown molecular mechanisms at play or other factors modulating the biological outcomes of editing.

This is the first study to suggest miRNA editing as an epigenetic mechanism underling asthma severity.

Model for A-to-I editing in children with more severe asthma.

particular target gene, called SOCS1, was overexpressed in most asthma cases compared to controls. Interestingly, this difference was observed for moderate and severe asthma, but not mild asthma. SOCS1 protein plays a role in suppressing some signalling pathways that are associated with immune responses. Although evidence is conflicting, most previous studies have indicated increased expression of SOCS1 is conflicting, most previous studies have indicated increased expression of SOCS1 protein plays a role in suppressing some signalling pathways that are associated with immune responses. Although evidence is conflicting, most previous studies have indicated increased expression of SOCS1.

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References


Funding

• National Institute of Allergy and Infectious Diseases
• National Heart, Lung, and Blood Institute

Collaborators

• Asthma Chicago Research (ACR) Study

Personal Response

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