Towards a cure for asthma and pulmonary disease

Dr Hiroaki Kume traces the physical sources of airway constriction and inflammation in debilitating and dangerous respiratory diseases, with the aim of overcoming the limitations of current treatment strategies.

What motivates the focus of your research into asthma and chronic obstructive pulmonary disease (COPD)?

Having worked as a physician in the field of respiratory diseases for 33 years, I have examined a lot of patients with asthma and COPD. When I first started out, it was difficult to improve symptoms and lung function, and avoid future risk of exacerbations and hospitalisations. Indeed, some deaths occurred. Then in the 1990s, inhaled glucocorticoid (ICS) therapy became widespread, and the situation improved to a certain degree. However, though effective, ICS is not a specific medicine for asthma and does not cure it. Moreover, there are no methods for establishing the cause of the disease for each patient.

Cross-sectional studies are needed to analyse the cause of asthma, and to find related molecules both for airway inflammation and airflow limitation. This may then reveal a therapeutic target. The same thing can be said about COPD, because airway neutrophil inflammation and airflow limitation are similarly implicated in this disease – currently, it cannot be cured completely and there is no specific anti-inflammatory agent for treating it.

Our explorations of the disease processes suggest target molecules for a novel therapy for asthma and COPD. I put my heart into this work, because I expect that the results from our basic research will be useful in the clinic.

Can you describe the limitations of current treatments for asthma and COPD?

The infiltration of eosinophils (white blood cells containing coarse granules) into the airways is part of the pathophysiology of asthma. Although in asthma ICS is administered daily, airway eosinophil inflammation is not always improved, and exacerbations can still occur. In COPD, bronchodilators are effective for improving symptoms and lung function to some degree, but do not prevent steady decline in lung function over time.

Why is airway remodelling such a serious problem in asthma sufferers?

There are no methods for examining airway remodelling clinically. Airway remodelling refers to the irreversible thickness of the airway wall, and is mediated by the proliferation and hypertrophy of smooth muscle and fibroblasts, and by migration of smooth muscle. This inhibits the response to medicines such as ICS and bronchodilators. Symptoms and lung function in patients with asthma tend to get worse, increasing exacerbations and hospitalisations.

Why is your finding that RhoA/Rho-kinase is involved in the pathophysiology of asthma so significant?

The expression of RhoA/Rho-kinase processes is enhanced in the respiratory system in patients with asthma and in allergen-challenged animal models of asthma. RhoA/Rho-kinase is distributed in many tissues, including those of the respiratory system. Activation of Rho-kinase contributes not only to sensitisation of contractile proteins to intracellular ionised calcium (Ca2+), but also regulation of cell differentiation and cytoskeleton reorganisation. These physiological reactions directly affect the contractility, proliferation and migration of airway smooth muscle cells, as well as the migration of inflammatory cells, leading to airflow limitation, airway hyperresponsiveness, beta-adrenergic desensitisation, airway remodelling and eosinophil infiltration to airways. As a result, RhoA/Rho-kinase may be closely involved with almost all the basic pathophysiological features of asthma. It has been revealed that airway smooth muscle cells may play an important role for the inflammatory processes implicated in asthma. So RhoA/Rho-kinase in airway smooth muscle is a novel molecular target in developing a treatment for asthma.

Do you have plans to translate your findings concerning Ca2+ dynamics and Ca2+ sensitisation in asthma and COPD into clinical applications?

Of course. However, there are some problems that must be resolved. For example, since agent-related Ca2+ signalling may cause adverse effects in the cardiovascular system, we would need to ensure that inhalants do not have adverse side effects. It might not be easy to develop inhalants with Rho-kinase inhibitors or Ca2+ blockers.

How do you see your research goals developing?

I am planning to continue my project on molecular biological methods. I would like to confirm that initial results from our research provide molecular targets to develop a novel therapy for asthma and COPD. Our goal over the next five years is to identify another key protein for both airway inflammation and airway obstruction that is involved in the fundamental pathophysiology of asthma and COPD – and to improve current medication for these diseases.
Asthma and a similar condition, chronic obstructive pulmonary disease (COPD), both manifest as difficulty with breathing. The number of people worldwide who suffer with asthma has increased dramatically over recent decades to an estimated 235 million today, with cases continuing to surge. In the same way that the aetiology of the disease remains a mystery, the reasons for its growing incidence are also unclear.

The long-held hypothesis that asthma is triggered by an immune system reaction to pollution or allergens is now being questioned, as its prevalence is rising across all geographical regions with widely disparate environmental conditions. In addition, about half of all asthma diagnoses do not involve allergic reactions. The disease now appears to be much more complex than originally thought.

On the other hand, the rising incidence of COPD – a condition encompassing chronic bronchitis, emphysema and chronic obstructive airway disease – is largely attributed to the ageing global population. It is anticipated that COPD will shortly become the third leading cause of death worldwide.

With both asthma and COPD characterised by airway inflammation and airway obstruction, it can be difficult to clinically differentiate between the two diseases, especially in elderly patients, and the result may be a diagnosis of ‘COPD-asthma overlap syndrome’.

INFLAMMATION IN BREATHING DISORDERS

In asthma, whatever its source, it is apparent that the immune system mounts an exaggerated response, possibly to environmental stimuli, which subsequently overactivates circulating immunologic cells. These are primarily granulocytes called eosinophils and T lymphocytes, although resident cells – such as fibroblasts and cells in the airway smooth muscle and epithelium – are also implicated. Eosinophils and airway smooth muscle cells induce hyperresponsiveness and airway remodelling; in fact, eosinophilic inflammation is the key hallmark of asthma. In COPD, the immune response leads to over-
NEW TARGETS FOR ASTHMA AND COPD THERAPY

Using his single channel recording technique, Kume discovered that both stimulatory and inhibitory G proteins, found in an enzyme called adenylyl cyclase, play a vital role in regulating $\kappa_C$ channel activity. The stimulatory G protein contributes to beta$_2$-adrenergic relaxation, while the inhibitory G protein contributes to muscarinic contraction – a functional antagonism that he thinks converges on $\kappa_C$ channels. These channels regulate the membrane potential, leading to Ca$^{2+}$ influx via voltage-dependent Ca$^{2+}$ (VDC) channels. Moreover, due to this channel linkage, Kume has also shown that Ca$^{2+}$ dynamics – together with Ca$^{2+}$ sensitisation due to RhoA/Rho-kinase processes – may contribute to airway obstruction, airway hyperresponsiveness, beta$_2$-adrenergic desensitisation, airway remodelling and eosinophil recruitment.

Kume has observed synergistic effects between beta$_2$-adrenergic receptor agonists and muscarinic receptor antagonists mediated by this channel linkage. He also notes that the combination of beta$_2$-adrenergic receptor agonists and muscarinic receptor antagonists in dual bronchodilator therapy improves both symptoms and lung function, and reduces exacerbations of COPD. Thus based on all of this evidence, Kume considers that the G protein/$\kappa_C$/VDC channel linkage and the RhoA/Rho-kinase processes are a highly promising molecular target for therapies for asthma and COPD.

recruitment of granulocytes called neutrophils, and, similarly, neutrophilic inflammation is a distinctive characteristic of the disease.

Treatment for asthma typically involves the use of an inhaler to administer inhaled corticosteroids (ICS), with pharmacological bronchodilators often taken alongside ICS to improve lung function. On the other hand, in COPD, pharmacological bronchodilators are primarily inhaled daily to improve lung function, with ICS often taken alongside pharmacological bronchodilators. Bronchodilation has little effect on inflammation in the airway walls, however. Plus it has been shown that ICS has no effect on cell proliferation or cell migration in airway smooth muscle, both of which inevitably exacerbate asthma – and there are concerns that prolonged ICS exposure induces adverse systemic effects, giving rise to eye problems and skin bruising.

As Professor Hiroaki Kume of the Respiratory Medicine and Allergology Department at Kinki University Faculty of Medicine in Osaka points out, the major limitation of both types of therapy is that they merely target the symptoms rather than the root causes of the diseases. “A novel therapy needs to be designed to reduce airway constriction, inflammation and remodelling, which should be established based on the pathophysiology of these diseases,” he asserts.

In his studies, Kume used an electrophysiological technique called single channel recording to study the characteristics of the large-conductance calcium-activated potassium ($\kappa_C$) channels that are densely distributed on the cell membrane of airway smooth muscle cells. His discoveries about $\kappa_C$ channel activity have enabled him to identify potential molecular targets for asthma and COPD.

PARALLELS WITH OTHER DISEASES

Due to the similarity of the pathophysiology of COPD and asthma with some other diseases, such as hyperlipidaemia, a useful approach is to explore strategies that have led to breakthroughs in understanding these other conditions. “Epithelial injury, eosinophil infiltration and smooth muscle hypertrophy are observed in the airway walls in asthma – and endothelial damage, monocyte infiltration and smooth muscle hypertrophy are also observed in the vascular walls in atherosclerosis,” Kume says.

For example, investigations have demonstrated that two compounds implicated in inflammation in atherosclerosis are regulated by RhoA/Rho-kinase processes – and they may also be involved in the pathophysiology of asthma. Interestingly, Kume also found that cholesterollowering drugs can have beneficial effects in asthma: “Our results have shown that statin suppresses proliferation of airway smooth muscle via inhibition of RhoA,” he states.

ADVANCING TESTING

In his investigations and tests, Kume has mainly used guinea pigs and rabbits as animal models due to the accessibility of their physiology. He is now keen to extend the scope of his work to explore the physiological processes involved in asthma and COPD at the molecular level. For this, he is planning to re-evaluate and potentially fundamentally rebuild his experimental system. As knocking out or over-expressing certain kinds of proteins are not currently available in guinea pigs, Kume plans to genetically manipulate mice to produce knock out and transgenic strains for future analysis. This throws up its own challenges, however; recording isometric tension and indicators of concentrations of intracellular Ca$^{2+}$ in the trachea of a mouse, or conducting a single channel recording of a single cell of tracheal smooth muscle would be extremely challenging, because the airway smooth muscle tissues of mice are so small.

Yet Kume is confident that he will overcome these logistical problems, and has already commenced with the design of a new experimental system. Ultimately, he hopes that his efforts will lead to clinical applications for human patients.

ESTABLISHING EFFECTIVE THERAPIES FOR ASTHMA AND CHRONIC OBSTRUCTIVE PULMONARY DISEASE

OBJECTIVES

To identify target molecules for novel treatments for asthma and chronic obstructive pulmonary disease.

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Hiroaki Kume obtained his MD from Toyama Medical and Pharmaceutical University in 1982 and completed his PhD in Respiratory Medicine at Nagoya University School of Medicine in 1990. Currently based at Kinki University Faculty of Medicine, he focuses on investigating the characteristics of airway smooth muscle using physiological methods, with the goal of identifying therapeutic targets for asthma and COPD.