MedicalXpress

Rage against the disease

August 5 2013, by Fiona Livy

Imagine a world where asthma wasn't a chronic disease, rather an inconvenient illness whose first symptoms could be easily treated. This vision could one day become a reality thanks to cutting-edge research into an immune receptor known as RAGE.

Though asthma was first discovered as far back as 450BC, the chronic inflammatory airway disease is still largely a mystery, says Senior Lecturer in the Graduate School of Health's School of Pharmacy Maria Sukkar.

"It's a disease that's triggered by various environmental factors like allergens and pollutants, and infections which can make it worse."

According to Sukkar, in 85 per cent of asthmatics the disease is triggered by an allergen. It's a process known as allergic sensitisation and inflammation. Essentially, "it's an immune-inflammatory response that develops to something in the environment that ordinarily wouldn't happen in someone who wasn't going to get asthma."

It's this process of allergic sensitisation that Sukkar and a team of researchers at the Woolcock Institute of Medical Research (WIMR) – Australia's leading respiratory and sleep research organisation – and the University of Queensland (UQ) are studying. The team includes UQ Senior Lecturer Simon Phipps, the WIMR's Carol Armour and Margaret Hughes, UTS's Matthew Padula and Steven Djordjevic and PhD students Md Ashik Ullah, Zaridatul Aini Ibrahim and Sharon Wong.

"What we've discovered is that a particular immune receptor in the lung, RAGE, is involved in this response."

RAGE stands for the Receptor for Advanced Glycation End products. Sukkar says, "It's been studied in cardiovascular disease, in diabetes, in arthritis. It has a long history in those conditions and the irony is that RAGE was first discovered in the lung about 30 years ago, but until recently, no one studied its role in airways disease."

Since Sukkar and the team started looking into RAGE five years ago, "our research has uncovered a role for this receptor in allergic sensitisation.

"What's novel about our research is that this receptor, once it's activated, can trigger the cascade of events in the immune response that drives the allergic inflammatory response that we see in asthmatic subjects. So we could say that asthma can develop as a result of the activation of this receptor by environmental allergens."

The next step, says Sukkar, "is to see whether this is a general mechanism that applies across any kind of environmental trigger." And "to see whether there is a genetic basis for this. That is, do genetic variations in the RAGE gene predispose a person to asthma?" To do this, Sukkar and her colleagues have teamed up with Professor in Pulmonology Dirkje Postma, from the University of Groningen in The Netherlands.

The potential public health benefits are huge. In Australia, asthma affects approximately 10 per cent of adults and up to 13 per cent of children. While the disease can be managed by anti-inflammatory inhaled corticosteroids, Sukkar says, "These drugs have to be taken on a daily basis, which as you can imagine, means a lot of people don't actually adhere to their therapy or adequately control their disease. We

really need to come up with new therapies that don't just control the symptoms, but induce the remission of the disease."

Sukkar believes RAGE could be a possible target for new drug therapies, including those RAGE-blocking drugs that are already being developed to treat cardiovascular disease, diabetes and arthritis.

Quite simply, says Sukkar, "For the last 20 years, there has been a lot of effort spent on developing drugs that target the immune pathways involved in asthma, but the problem is we now realise we were targeting the end of the pathway; that is shutting the gate once the horse has bolted. What's exciting about our research is we think we've found something that's key in triggering this process.

"We know the process of sensitisation is absolutely fundamental to the disease; it's the strongest risk factor, but we still don't understand why this process happens. If you can understand the mechanism you can start to understand the 'whys'. The 'whys' are probably because there's a genetic basis and an environmental basis and the two have to meet; you have to have this set of genes and meet this allergen and 'boof' you've got asthma.

"Some people go into remission, but most people don't. It's one of these conditions that is highly prevalent and it impacts on quality of life and it's still potentially fatal – there are over 400 deaths in Australia from asthma per year."

In yet another boost to this research, later this month the School of Pharmacy will welcome Sukkar's former postdoctoral supervisor at the National Heart & Lung Institute at Imperial College London (and a world leader in asthma research) Professor Kian Fan Chung as a Distinguished Visiting Scholar.

"Collaboration and connection with other researchers is critical," says Sukkar. "Our findings so far, are primarily based on studies in mice, and this work was done at the University of Queensland. What we're doing now, in my lab here at UTS, is trying to show what we've discovered in the mouse is relevant to the human disease.

"Several PhD students are currently advancing this work. What we are doing now is getting cells from human lung tissue and exposing them to allergens and other asthma triggers to see if we can replicate our findings in human lung cells.

"This kind of work is fundamental; you can't go from the mouse to a drug. If you do you'd probably miss something major. You have to understand the process and there's a lot more to understand about this pathway. As exciting as it is, we're really just at the beginning."

Provided by University of Technology, Sydney