The curious relationship between diseases and immune systems

Dr Tom Monie conducts investigations into the innate immune signalling process. Below, he discusses his inspirations and contributions to certain syndromes, and highlights some fascinating work he has undertaken regarding cat allergies.

What inspired you to focus your research on the immune system and how it correlates with infectious disease and inflammatory conditions?

I have always been interested in infectious diseases and how the host interacts with pathogens. I find the dynamic nature of this interaction intriguing. Early in my career, I was more interested in the pathogens themselves. However, it soon became apparent that understanding how the host uses proteins to defend against infection presented a better chance of contributing towards basic science research that could ultimately be used to improve treatment options against a wide range of infections and inflammatory diseases.

Proteins represent the business end of cellular function. They control what the cell can and cannot do. In many ways, they are like flexible 3D jigsaws in which every piece has a particular role to play. Some of these roles are so important that if you change one piece the protein might stop working, or how it works might change. Other pieces can be changed with little, if any, functional impact.

Can you describe the overarching aims of your research at present?

The main aim is to understand how receptors such as NOD1 and NOD2 communicate with their adaptor proteins (RIPK2, CARD9) in the cell to mediate the inflammatory response. This is done through interactions between caspase recruitment domains (CARDs) in the protein structure. If we manage to extend our current work and identify the exact interactions occurring, we have the potential to design specific molecules and small peptides to disrupt or enhance this interaction. I am also interested in comparing cross-species functionality in the immune response. Seeing which amino acids are conserved between species can be immensely insightful when it comes to understanding their function and role.

How could your research on Blau syndrome contribute to the development of more effective therapeutics?

My work on Blau syndrome has helped to demonstrate that this disease results from dysregulation of the control of NOD2 signalling. Specific mutations in NOD2, often referred to as polymorphisms that occur within the central domains of NOD2, stop the protein from being able to maintain an auto-inhibitory shape in the absence of stimulation. Therefore, this causes NOD2 to send pro-inflammatory signals – even in the absence of ligand stimulation and produces the chronic inflammation observed in Blau syndrome.

Identifying how these mutations fit in the molecular structure, as well as the other parts of the protein that they interact with and how they might alter NOD2 function, could lead to the development of new therapeutics aimed at turning off NOD2 signalling. These could be small molecules, or peptides, that either restore the inhibition of NOD2 activation, or that stop downstream signalling, such as the interaction of NOD2 with its adaptor protein RIP2K. I think the second option is more feasible.

Your research into cat allergy has received global media attention due to the fact it could lead to new and improved treatments for sufferers. Can you provide details?

The work on cat allergy followed on from work we had done looking at why TLR4 (the cell surface receptor for bacterial lipopolysaccharide and important in sepsis caused by Gram negative bacteria) from different species responded differently to different types of lipopolysaccharides.

Other groups had shown that TLR4 could be activated by the house dust mite allergen and we were interested to see if this was the case for other major allergens. We found that both the cat and dog allergens could also increase TLR4 signalling and therefore enhance inflammation. If this can be controlled, it might reduce the airway inflammation induced by the allergen, thereby reducing the symptoms.

Finally, what led you to this work and to your collaboration with Professor Clare Bryant, the lead author of this study?

Professor Bryant is also interested in understanding how the innate immune system works in disease, particularly in response to bacterial infection. Our collaboration is long-standing, productive and came about because we have highly complementary research interests and tools. Her research is more focused on the cellular and whole organism responses to infection, the pharmacology of immune signalling and the use of new microscopic techniques to visualise immune signalling complexes.

My interests centre more on the molecular level and involve building a better understanding of exactly how the proteins work and interact with their ligands and one another. I do this using a range of computational and recombinant protein approaches. When combined, these provide a much more complete understanding of the innate immune signalling process.
THE IMMUNE SYSTEM is a complex network of structures and processes within the body that protects against disease and wards off a variety of threats. The human body is an attractive site for a range of pathogens – and the immune system has to work continuously to either prevent them from entering the body or to destroy them if they manage to gain entry. The relationship between pathogens and the host is a fascinating game of one-upmanship, where the threats evolve to bypass the immune response and our defences constantly learn to recognise these changes in order to maintain protection.

However, the immune system does not always perform its duties in a successful way. In a healthy body, when something considered ‘foreign’ comes into contact with the immune system, the defence launches an attack. Cells or organisms that trigger such a response are known as antigens. Unfortunately, there are situations where the immune system does not perform this function. Indeed, there are instances where it attacks the body’s own cells, resulting in autoimmune diseases such as type 1 diabetes.

IDENTIFYING TARGETS OF CONTROL
The immune response begins when molecular danger signals activate proteins known as pattern recognition receptors. However, the precise mechanisms involved in such interactions are not fully understood. If light can be shed on such processes, scientists would be able to identify potential targets for therapeutics to modulate immune function, thereby helping to control and treat disease. Dr Tom Monie is based at the Medical Research Council Human Nutrition Research Unit in Cambridge – and he performs research that seeks to uncover how specific proteins interact with the mechanisms that underlie infectious diseases and inflammatory conditions. Much of his current work is focused on the role nucleotide-binding oligomerisation domain-containing protein (NOD) 1 and 2 play in combatting bacterial infection and maintaining cellular homeostasis. “I find the protein-protein interaction surface fundamentally beautiful,” explains Monie. “Proteins often communicate through physical contact, allowing them to send messages through the cell that lead to functional changes, such as turning the innate immune response on and off.”

DOUSING INFLAMMATIONS
If Monie is able to advance understanding of the precise ways in which NOD1 and NOD2 receptors are turned on, this would prove highly relevant to the development of vaccines for a range of infectious diseases. Indeed, the design of therapies specific to these receptors could have the potential to inform the inception of treatments to reduce inflammatory conditions induced by bacteria, as well as diseases such as Crohn’s disease and Blau syndrome.

With these aims in mind, Monie has collaborated with the University of North Carolina’s Dr Alex Duncan to determine exactly how NOD2 interacts with its ligand muramyl dipeptide to initiate signalling. “Muramyl dipeptide is derived from peptidoglycan in the bacterial cell wall,” explains Monie. “We have preliminary data suggesting that NOD2 may not actually detect bacterial peptidoglycan in all species which suggests some interesting evolutionary developments.”

In addition to these findings, Monie has shown how polymorphisms in NOD1 and NOD2 influence the function of these receptors, thereby providing important insights into how signalling is disrupted. Understanding such disruptions is highly relevant to the study of inflammatory diseases, particularly their ability to detect and respond to bacteria, and the regulation of normal cell signalling.
IMMUNE SYSTEM ACTIVATION

OBJECTIVE
To understand how receptors such as NOD1 and NOD2 communicate with their adaptor proteins in the cell to mediate the inflammatory response.

KEY COLLABORATORS
Professor Clare Bryant, University of Cambridge, UK
Professor Jonathan Powell, Medical Research Council Human Nutrition Research, UK
Professor Thomas Kufer, University of Hohenheim, Germany
Dr Joseph A Duncan, University of North Carolina at Chapel Hill, USA
Dr Katrin Rittinger, The Crick Institute, UK

FUNDING
Medical Research Council
Wellcome Trust (past)
Biotechnology and Biological Sciences Research Council (past)

CONTACT
Dr Tom P Monie
Medical Research Council Human Nutrition Research Unit
Elsie Widdowson Laboratory
120 Fullbourn Road
Cambridge
CB1 8BL
UK
T +44 1223 437 665
E tpm22@cam.ac.uk
http://bit.ly/1SPVzjA
www.researchgate.net/profile/Tom_Monie
www.linkedin.com/in/tom-monie-2506b174
@Tom_Monie

TOM P MONIE received his PhD from the University of Cambridge. During this time, he was honoured with the biennial Young Investigator Award from the International Retrovirology Association for HTLV and Related Viruses in recognition of his seminal work in this field. Monie had subsequent postdoctoral positions at Imperial College London and the Department of Biochemistry at the University of Cambridge. Between 2008-14, he held a prestigious Wellcome Trust Career Development Fellowship that enabled him to set up his own research group. In 2014, he moved to the Medical Research Council Human Nutrition Research Unit.

The team has also begun to understand how both NOD1 and NOD2 signal in the cell, especially in terms of the ways they interact with the adaptor proteins RIPK2 and caspase recruitment domain (CARD) 9. This presents a potential means of identifying targets for immunomodulating therapeutics, as well as for discovering how they communicate with other immune signalling pathways.

STUDYING INTERACTIONS
It is known that CARD interactions are common in both immune and death-related signalling pathways in cells, Monie’s research has also turned his attention to uncovering more about these interactions. “If we understand how these interactions take place, then we are moving closer to knowing how the proteins transfer messages in the cell,” he explains. “In particular, we will know exactly which surfaces interact with each other and then we can target these with small molecules or peptides in order to modulate the signalling responses to stimulation.”

The researchers have characterised the main interface involved in interactions between NOD1 and RIPK2 – and, interestingly, it appears that it is different from the one used in the case of interactions between NOD2 and RIPK2. These findings could signal a means of designing therapeutics that hone in on one particular pathway whilst ignoring the other. There is more work to be done in this area, but the team is certainly headed in the right direction. “One possibility is that NOD1 and RIPK2 form a larger structure in which lots of CARDs come together to form a signalling complex,” says Monie. “What is clear is that the process of NOD1 signalling is more complex than previously thought.”

SIGNALLING A WAY FORWARD
Monie’s work thus far has contributed to a much more complete understanding of the innate immune signalling process and boasts huge potential for improving treatments for infectious diseases and inflammatory conditions. Future investigations will attempt to uncover the ways in which proteins transfer messages within cells. Ultimately, determining such intricate mechanisms will enable the modulation of signalling responses to stimulation, potentially transforming the lives of millions of people around the world.