Pathways and pathogenesis

Professor Tim Palmer is investigating the role that cytokine signalling processes have in the development of cardiovascular disorders, and the effect that turning these processes off could have on disease progression.

You have spent your career at the interface of biology and chemistry. How have your research interests and activities developed over the years?

My early interest in how hormones work led to a fascination with cell signalling pathways and how they are controlled. As a result, for my PhD project I chose to focus on identifying defects in cyclic adenosine 3’,5’-monophosphate (cyclic AMP) signalling in liver and adipose in models of type 2 diabetes. However, while this was interesting, it soon became clear that understanding these pathways in detail required the application of molecular and cellular biology approaches. I was fortunate to gain these skills during postdoctoral research studies within the Cardiology Division at Duke University Medical Centre in North Carolina, USA, where I examined the molecular mechanisms responsible for the ‘desensitisation’ – or switching off – of adenosine receptor subtypes expressed in vascular smooth muscle and endothelial cells.

How did your research journey lead you to begin creating treatments for cardiovascular disease?

Not long after starting my own research group at the University of Glasgow, UK, my team began to apply the approaches previously described to examine the regulation of sphingosine-1-phosphate receptors (SIPRs) expressed in endothelial cells. These receptors are now found in immunosuppressant drugs that are used to treat multiple sclerosis. It also became apparent that chronic localised inflammation of endothelial cells lining large blood vessels was an important step leading to the atherosclerotic plaque formation that can result in heart attacks and strokes. Therefore, we began to look at how adenosine receptors could block these events, and this has led to some of our current research programmes that are examining how cytokine signalling processes can be turned off.

Can you describe your examination of these inhibitory pathways and elaborate on how they are regulated?

We are examining two pathways that block cytokine receptor signalling. One of these involves the suppressor of cytokine signalling 3 (SOCS3). While normally expressed at low levels, SOCS3 expression is induced...
by cytokines such as IL-6, and binds to the signalling component of the IL-6 receptor complex to inhibit subsequent downstream signalling as part of a negative feedback loop. However, SOCS3 is also induced by other hormones, including those that increase levels of the intracellular messenger cyclic AMP. By analysing the SOCS3 gene, we have identified a new pathway by which cyclic AMP could increase gene transcription. We also uncovered how it could suppress pro-inflammatory IL-6 responses in endothelial cells. Following on from this work, we employed proteomic approaches to identify previously unknown SOCS3-interacting proteins that control its stability and function.

**Your other area of focus is AMP-activated protein kinase (AMPK), a master regulator of cellular metabolism. What have your studies in this area uncovered?**

AMPK, which is targeted by anti-diabetic drugs such as metformin and thiazolidinediones, has well described anti-inflammatory effects, but the mechanisms underlying these remain unclear. Using biochemical and molecular biological approaches, we have identified a new mechanism by which AMPK can turn off signalling from multiple cytokine receptors by directly phosphorylating a common post-receptor intermediate.

Not only might this provide one possible explanation for the protective effects of drugs such as metformin, which reduce the risk of cardiovascular disease in diabetics, but it may also inform the wider repurposing of these drugs for other diseases with a chronic inflammatory component.

**How would you like to see your scientific activities progress with your recent move to the North of England?**

One of the reasons I relocated to the University of Bradford is that there were several areas of research at this institution I felt I could contribute to, and that will also bring new approaches to my own research programmes. For example, I have a strong interest in neurodegenerative disorders such as Alzheimer’s and Parkinson’s diseases, which are now known to be associated with a strong cytokine-driven neuroinflammatory response. As well as providing insights into disease progression, understanding how this operates at the molecular level may also enable the identification of drug targets that slow the neurodegenerative process. Finally, given that management of excessive inflammation is required in many diseases, it is difficult to predict in which direction our research will ultimately go – something that makes it all the more exciting!

**THERAPEUTIC DEVELOPMENTS**

Indeed, the basic research in Palmer’s lab has significant therapeutic implications. The researchers have pinpointed key sites within the sphingosine-1-phosphate receptor 1 (S1PR1) that are phosphorylated in response to certain stimuli, and have subsequently identified that the phosphorylation of these residues causes the internalisation of S1PR1 away from the plasma membrane. “Using the molecular tools developed by myself and my colleagues, a research group in Naples, Italy, has shown that S1PR1 can interact with the beta-adrenergic receptor – a target for beta-blocker drugs used to treat heart failure – and that the conditions triggering the internalisation of one receptor also cause internalisation of the other,” Palmer reveals. “Importantly, these observations suggest that S1PR1 and the beta-adrenergic receptors reciprocally regulate each other via a mechanism involving receptor phosphorylation.” As a result of these findings, the team in Naples is currently exploring the potential use of S1PR1 in cardiac gene therapy.

In addition, the researchers have identified mechanisms that show S1PR1 can enhance the survival of endothelial cells, with subsequent studies revealing that this happens as a result of S1PR1’s activation of the MAP kinase and PI3 kinase pathways. Recent investigations using fibroblasts have highlighted that S1PR1 are promising targets for breast cancer therapies. Indeed, Palmer points out that S1PR1-selective antagonists could have the capacity to block several pro-survival pathways in both tumour cells and the endothelial cells within the tumour vasculature.

**CALLING FOR COLLABORATION**

Moving forwards, Palmer and his colleagues are planning to redouble their collaborative efforts with other scientists, using their combined knowledge and expertise to drive the development of new therapeutic strategies for a range of deadly cardiovascular conditions. For instance, one of the team’s major areas of focus at present is pulmonary arterial hypertension (PAH), a disease characterised by the thickening and stiffening of the pulmonary artery walls. They are working closely with researchers from Cardiff University and the University of Glasgow to ascertain how the reduced inhibition of IL-6 responses by SOCS3 impacts the progression of this disease. With very few treatments currently available for PAH, the scientists are eager to test whether the SOCS3-mediated inhibition of IL-6 responses could be an important therapeutic mechanism. Looking ahead, Palmer’s team is also aiming to work with other UK-based collaborators to determine the role of the AMPK pathway in inhibiting cytokine signalling in rheumatoid arthritis.

**INTELLIGENCE**

**MOLECULAR MECHANISMS THAT UNDERPIN CHRONIC VASCULAR INFLAMMATION IN THE PATHOGENESIS OF CARDIOVASCULAR DISEASES**

**OBJECTIVE**

To explore inhibitory pathways that block cytokine receptor signalling, with a view to developing new therapeutics that prevent the development of vascular dysfunction that can cause heart attacks, strokes and pulmonary diseases.

**KEY COLLABORATORS**

Dr Ian Salt, Professor Mandy MacLean, Professor Andrew Baker, University of Glasgow, UK
Professor Simon Jones, University of Cardiff, UK
Dr Giuseppe Rengo, Federico II University of Naples, Italy
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**FUNDING**

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