Vital vessels

Experienced physiologist and blood vessel researcher Dr Geoffrey Payne reflects on his career in the field, and explains his current research towards understanding microvascular networks and their role in maintaining our overall health.

What attracted you to the field of microcirculation and your work on ageing?

I began my research career evaluating brain microcirculation – looking at how the onset of stroke impacts the microvessels that promote this disease. Stroke has long been a disease associated with ageing, and a more complete understanding might lead to new theories that could inform novel therapeutics. The question of ageing and impacts on microcirculation fuelled my interest and led me to move to Yale University to begin evaluating the microcirculation in skeletal muscle under the guidance of Dr Steven Segal.

Skeletal muscle comprises a significant component of the human body and therefore any impact on the microcirculation supplying these muscles leads to a decrease in function and potentially the onset of such diseases as diabetes or hypertension. My work in the area led to new insights on the role of the immune system. If the microvasculature that feeds the tissues and organs regulates blood flow to ensure a supply of vital oxygen and nutrients, as well as the key signalling mechanisms that are integral for this regulation. More importantly, I aim to uncover how these key signalling mechanisms are impacted by disease states affecting the microcirculation and ultimately how these diseases change microcirculatory function and promote the onset of symptoms. My view is that we learn about normal physiology in order to inform our understanding of pathophysiology.

Your current project focuses on microvascular networks. What are your chief aims and mission?

Recently, I have moved my evaluation of the microcirculation away from skeletal muscle and towards the lymph nodes, in the hope of elucidating the links between vascular biology and immunology – two fields that do not intersect nearly as often as they should. The goal of the current project is to understand how viruses impact the arterioles, which are the microvessels that deliver blood to tissues and organs and in this case feed the lymph nodes. I want to understand how viral impact on the arterioles affects immune function and if there is an interplay between the two within an immune response, thus vascular immunomodulation.

How does your research project contribute to understanding of the human immune system?

It allows us to begin thinking in terms of novel methods for the modulation and modification of the immune system. If the remodelling processes that we have described in our recent published work are indeed, as we believe, vital to a normal immune function, then we can begin to think of how we could manipulate that function in certain cases improve immune responses. This might have applications, for example, in the case of immunocompromised individuals, whose response to viral infection could be modulated to decrease the impact of the virus. The ageing population is one of the most immunocompromised groups that exist and it will therefore be a focus of our work.

Have collaborations with other organisations helped progress this work?

During my tenure at Yale University, I have been extremely grateful for the guidance of Dr Segal, who is now at the University of Missouri. He allowed me to change the way I think about the microcirculation. Dr William Sessa of Yale University was also instrumental in helping me to think about the signalling mechanisms that impact the microcirculation. Finally, Dr Akiko Iwasaki was my collaborator on the vascular remodelling project and helped to bridge my microvascular research with her immunology work.

How do you foresee your research progressing over the next five years?

The next few years are going to be taken up with work towards improving understanding of this immune-induced vascular remodelling and determining whether or not it holds consistent across multiple viruses and in various lymph nodes.

As I look forward to the work that lies ahead I would like to take this opportunity to thank International Innovation for the chance to share my thoughts on my research. It is only through opportunities such as these that we can continue to ask the right questions and create new ideas for study. True knowledge, in my opinion, comes from asking questions – and questions that come from the experience of multiple disciplines ensure that new knowledge continues to inform new research. This, I think, is the very foundation of science.
A healthy circulation

A group of researchers at the University of Northern British Columbia, Canada, is studying the remodelling of microvascular networks in response to viruses with the aim of gaining an insight into how this remodelling is key to the immune response.

THE CIRCULATORY SYSTEM in its simplest form is a circuit of pipes connecting the organs, with blood driven around by the pressure of an indefatigable pump – the heart. Science does not know exactly how many cells are in the human body, because they are extremely varied and difficult to count – but most estimates put the number in the tens of trillions, and all need a supply of blood to receive nutriment and dispose of waste. In order to achieve adequate circulation at a cellular level, the body makes use not just of the veins and arteries, but also the much smaller blood vessels of the microvascular networks – the arterioles and venules. These smaller networks are responsible for the distribution of blood within each organ.

Unlike veins and arteries, the diameter of which can be measured in millimetres and centimetres, the vessels of the microvascular system are extremely small – on the μm scale. These tiny channels, which can be less than 1/20 the diameter of a hair, ensure that all the constituent cells within an organ receive the blood supply they need. To fulfil its function, the microvascular system must be a dynamic arrangement, not a rigid one. In order to control cardiac output locally, the vessels are capable of dilating or contracting in response to certain hormones and Ph levels in the bloodstream, and networks have been known to remodel themselves in the context of disease.

MICRO BUT MIGHTY

The microvascular system is therefore an important component in the body and crucial to health – but its mechanisms of growth and change are still not very well understood. A number of disease states have been integrally linked to changes in the microvascular system, and many of these diseases – such as stroke – are associated with ageing. It seems that the aged microvascular system changes its operations, but since little is known about the normal function of these networks, there is no starting point for determining the effects of their...
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abnormal function. Circulation plays a role in diseases which affect every part of the body, so there is a great incentive to discover more about any microvascular network, producing results that could be applied across the board.

One group has been studying these fascinating yet miniscule networks for many years, in the context of varied organs and diseases. Dr Geoffrey Payne leads the Vascular Immunology Laboratory at the University of Northern British Columbia in Canada, in addition to his duties as Assistant Dean for Education and Research and an Associate Professor of Physiology. The aim of the research programme carried out by the lab is to understand the impact of diseases and disease states on microcirculation, with a view to ultimately discovering routes towards new therapeutic approaches for these conditions. Recently, Payne and his collaborators have used their tried and tested methods to bring to light a number of new discoveries in the field of vascular health.

METHODS AND APPROACH

In order to study microvascular networks, Payne makes use of intravital microscopy techniques – methods whereby a window preparation can be attached to an animal model in order that the biological system for study can be easily observed in real time – as well as a number of other novel in vivo imaging methods. It was by using such methods to examine microcirculation in mice that Payne and his collaborators previously discovered that cell-to-cell communication in the microcirculatory system is conducted through the endothelium, and that in cases of inflammation this communication breaks down. Similarly, the researchers showed that in aged microvascular systems the communication between cells is also less than usual – a reduction responsible for less oxygen and nutriment reaching the cells, possibly causing disease states such as diabetes and hypertension.

A SURPRISING DISCOVERY

The team’s work has primarily focused on microcirculation in different parts of the body in the context of a number of diseases and recently they have had particularly interesting results from studies on lymph nodes. The lymph nodes have a number of functions relating to the immune system, but perhaps the most prominent is in the production of antibodies; plasma, lymphocytes and other antibody-presenting cells are carried in the lymph, and they build up in the lymph node in cases of immune response, causing it to swell. Of late, Payne’s group was successful in characterising, for the first time, lymph node vascular growth – showing that arterioles feeding the inguinal lymph node remodel themselves in response to the presence of a virus. The arteriole actually grew when the virus was present in the system, subsequently enlarging the lymph node itself, and the surprising reaction was that it was seen to be reversible, and therefore non-pathological.

This response makes perfect sense as a measure to prevent disease – more blood to the lymph node means a higher number of antibodies are created and the immune system’s ability to combat the intruder is bolstered. It is surprising, however, because it is the first example of microvascular remodelling as part of a healthy immune function and not as part of disease pathology. The researchers have subsequently shown that both vascular and immunological signalling systems are integral to the precipitation of this remodelling event, demonstrating conclusively that this process is not a symptom, but a legitimate response. This conception of microvascular modelling is an exciting development, representing a new way of thinking in this field.

CHANGING WITH AGE

Based on this success, the British Columbia team turned its attention to the effects of microvascular remodelling on ageing. With age, the ability to fight off infections is reduced, an incapacity that can be highly detrimental to the health of older people. Payne’s collaborators hypothesised that if microvascular remodelling was indeed part of a healthy immune system, it could have a role to play in reducing an older person’s ability to fight infection. The group’s studies confirmed that this was the case; the ageing process is detrimental to the microvascular system’s modelling capability, and this has a knock-on effect on the progression of infection.

The next step for the researchers will be to study the signalling mechanisms involved in this remodelling process. Their previous studies have allowed them to identify a number of signals as being responsible for remodelling, and they are now in the process of advancing this picture towards completion. Ultimately, the aim will be to have a full understanding of the signalling involved – at which point it may be possible to gain control of that signalling, and then harness this control in new therapeutic treatments. Science has long known that the microvascular system is vital to health, but now it is known that the remodelling of that system is also crucial. Perhaps this new understanding will lead to solutions to enhance health, preserving it for longer than is currently possible.