As blood pressure rises, cells struggle to cope with the strain, releasing cell contents which act as alarm signals to the immune system.

Dr Clinton Webb and colleagues at the Department of Physiology at the Medical College of Georgia at Augusta University, are investigating how this promotes inflammation, resulting in further blood pressure rises and the development of a dangerous feedback loop.

"The more blood pressure goes up, the more injury you have," says Dr Webb. He and his colleagues want to gain a better understanding of the signalling pathways involved in this type of inflammatory response so that treatments can be tailored to an individual’s needs. "It’s a circle," says Dr Webb, "in which inflammation is a constant and which isn’t addressed in today’s treatment regimens."

Dr Webb is a vascular expert, Chairman of the Department of Physiology at the Medical College of Georgia at Augusta University. He is also the Herbert S. Kupperman Chair in Cardiovascular Disease and was named a Regents’ Professor in 2011. In 2013 he was the recipient of the American Heart Association Council on High Blood Pressure Research’s Irvine Page-Alva Bradley Lifetime Achievement Award for his work in the field of hypertension. He is now the principal investigator on a $9.4 million Program Project Grant from the American National Heart, Lung and Blood Institute, specifically aimed at identifying how cellular debris contributes to this unhealthy phenomenon.

CRACKING UNDER THE STRAIN

It’s clear that higher blood pressure, from causes like obesity and salt sensitivity, increases cell death. Smooth muscle cells and endothelial cells that comprise the blood vessels are the first casualties. “There is no doubt there are more dead cells in the hypertensive blood vessel,” Dr Webb says. Once outside the dying cell, typical cellular contents such as DNA and its partner protein HMGB1, which helps stabilise the DNA, are categorised by the immune system as ‘damage associated molecular patterns’, or DAMPs.

DAMPs can be thought of as the body’s alarm signals, because they resemble fragments from bacterial or viral invaders. In

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The case of an infection, these signals set in motion essential immune and inflammatory processes which organise to repel the invader. Side effects of this heightened immune activity are blood vessel constriction and kidney damage, to name but a few, which result in more cell death and release more DAMPs into the system.

The current project is looking closely at a very specific sub-set of actions, those resulting from the release of DNA from mitochondria in blood vessel endothelia (the cells lining the internal surface of the vessel). This DNA, which comes exclusively from the mother and has not been mixed during fertilisation, is therefore distinctly different from that of the organism and so not recognised as ‘self’.

FOLLOWING THE ACTIVATION PATHWAY

This specific element of DAMPs is a potent activator of TLR-like receptors, or TLRs. These are found inside many cells and the nine different types have in common some degree of activation of MYD88, a downstream signalling molecule which in turn activates transcription factor NF-κB, responsible for controlling gene expression as well as programmed cell death. TLR4 in particular, is linked to the necessary initiation of inflammation in response to membrane components of bacteria. Inside blood vessels, when excessive cell death leads to the release of mitochondrial DNA, it can start to activate TLRs inside immune, vascular smooth muscle or endothelial cells. One of many questions the researchers want to answer is whether TLR4 and TLR9 have some unfortunate inflammatory synergy through their activation of MYD88 in this scenario.

A TEAM EFFORT

Within the team, project leaders Drs Jennifer Sullivan and Paul O’Connor, respectively, are exploring how the different ways cells die in males and females impact the damage that follows the release of HMGB1, and how an onslaught of these and other DAMPs cripples the kidney’s ability to help regulate blood pressure.

Dr Adiyya Ergul, a vascular physiologist, is managing the bioinflammation core, and Dr Michael Brands, a cardiovascular-renal physiologist, is managing the animal model and instrumentation core for the five-year studies, to ensure the consistency of results gathered and minimal animal usage.

This is not ‘blue skies research’. Globally, the overall prevalence of raised blood pressure in adults aged 25 and over was around 40% in 2008, and the World Health Organization estimates that raised blood pressure is the cause of 7.5 million deaths worldwide every year. Webb thinks DAMPs are both the result and initiators of hypertension in many of these cases.

The long-term goal of Dr Webb and his colleagues is to identify targets that could block some of the unintended results without compromising an efficient natural immune response. “Imagine, for example, if you could figure out a drug that would actually block the uptake of mitochondrial DNA,” Dr Webb says. Or, in the case of his colleague Dr Sullivan, a pharmacologist and physiologist, a drug that reduces excessive activation of T-cells, the drivers of the immune response. Either of these could be therapeutically important.

SEX CELLS

The difference between the sexes is also significant. High blood pressure in males tends to kill cells through necrosis, whereas before the age of menopause, females experience more apoptosis, or programmed cell death. The first leads to the rupture of cells and release of internal molecules, the second to a controlled cell elimination that better contains cellular debris. Apoptosis is also to an extent anti-inflammatory, so although both sexes suffer from hypertension, their respective pathways may be substantially different. Knowledge of how this impacts the disease is vital for effective personalised treatment strategies.

A specific aspect of this project is enabling the researchers to further investigate the differences between cell death in male and female models of the disease. This will allow them to see the effects on blood pressure regulation and immune system activation of inhibiting cell death. They are particularly interested in what happens in the kidneys – which cells are affected and whether the immune system activates in response.

BREAKING THE BLOCKADE

The kidneys have a vital role to play in managing fluid volume and hence blood pressure, by regulating the production of urine and retention of vital salts. To do so, it needs to be infused with narrow blood vessels which can facilitate the rapid reabsorption of essential substances. The downside is that these narrow vessels are susceptible to becoming clogged with the relatively large red blood cells passing through them, a problem overcome by the presence of contractile pericytes. The team are exploring whether DAMPs interfere with the pericytes’ ability to contract, creating blockages which disrupt kidney function and drive up blood pressure. If this theory, and the early evidence on which it is based, hold, drugs which support these contractile cells could enable the kidneys to remain helpful in avoiding hypertension.

The vast capacity of the kidneys means that related problems do not usually become apparent until about 80% of function is lost. For this reason, the team are investigating whether endothelial cells that line the unusual vasculature are stimulated by DAMPs to make more of the blood vessel dilator nitric oxide, which weakens the contractility of pericytes.

The researchers are pushing forward on many fronts as they search for solutions to a complex problem continues. “We are trying to identify whether DAMPs play a role in the hypertensive process. I think that is the fundamental question,” Dr Webb says of the extensive studies ahead.

How does the team impact on the ability to make progress in these complex research areas?

The impact of a team in science is much like anything else. Each individual brings something different to the program and this has a way of making everything better. The more “brains” in the room, the better the outcome!

What do you hope to achieve over the course of this particular project?

Our goal is to characterise the role of damage-associated molecular patterns in the blood pressure elevation that is characteristic of hypertension.

What is unique about this aspect of hypertension research?

The unique aspect of our work is the intersection of cardiovascular disease with inflammation.

How has your personal experience of inflammatory disease influenced your research?

This one is easy. I have been very lucky – I’ve had no personal experience with any inflammatory disease. Actually, I have not had any medical problems – just the common stuff.

FUNDING

• National Institutes for Health (NIH)

BIO

Dr Clinton Webb was awarded his BA and MS (Physiology) at Southern Illinois University and his PhD (Anatomy) from the University of Iowa. He completed his postdoctoral studies in Michigan and Antwerp. He is fellow of the American Society of Hypertension and Distinguished Research Faculty member at Augusta University Graduate School.

CONTACT

Dr Clinton Webb
Department Chair, Physiology, Medicine Kupperman Chair in Cardiovascular Disease, Physiology, Medicine Regents’ Professor, Physiology, Medicine Medical College of Georgia Augusta University 1141 15th Street CA 3123 Augusta, Georgia 30912-4050 USA

E: CW Webb@augusta.edu
T: +1 706 721 7742
W: http://www.augusta.edu/mcg/phy/ faculty/shps_faculty_webb.php

RESEARCH OBJECTIVES

Dr Clinton Webb specialises in the vascular physiology and pathophysiology of hypertension. His current research focuses on the investigation of the role of damage-associated molecular patterns (DAMPs) in vascular inflammation and endothelial dysfunction in hypertension. Dr Webb is principal investigator on a large Program Project Grant from the National Heart, Lung and Blood Institute, that aims to understand how cell death from high blood pressure fuels a vicious cycle of even higher blood pressure.

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