Vascular investigations

Dr Zhihong Yang discusses his longstanding research interest in endothelial dysfunction in vascular ageing and disease, and outlines his efforts to elucidate the underlying mechanisms involved.

Can you provide a brief outline of your academic career and research interests?

I studied medicine in China and graduated in 1986. The following year, I received a stipend to come to Switzerland and work with Professor Thomas F Lüscher on cardiovascular diseases. I ended up spending more than 10 years at the universities of Basel, Bern and Zürich. Since 2000, I have been working as Associate Professor in physiology at the University of Fribourg. My long-term research interest is endothelial dysfunction in vascular diseases such as atherosclerosis. Since moving to the University of Fribourg, my research focus has expanded to obesity-associated insulin resistance, type 2 diabetes, and organismal ageing and age-related diseases.

What are the key objectives of your lab’s ongoing research?

Our key objective is to explore underlying mechanisms that link inflammation, oxidative stress and accelerated cell senescence in the ageing process, and elucidate how these mechanisms contribute to the development of age-associated diseases and organ failure, including cardiovascular disease, type 2 diabetes, and liver and kidney diseases.

How can better understanding of the causes of vascular ageing advance treatments for its associated diseases?

Since the pathogenesis of cardiovascular diseases, diabetes and the ageing process have common mechanisms, I am confident that identification of the causes of cardiovascular diseases and/or diabetes will help us to understand the mechanisms of these diseases and organism ageing. Therefore, targeting these common mechanisms will slow down disease development and delay the ageing process, resulting in a prolonged healthy ageing period (improved life quality in advanced age) and, eventually, extended lifespan.

Could you explain the genetic and environmental causes of unhealthy vascular ageing?

There is no doubt that genetic factors determine ageing as well as cardiovascular disease. Children with Hutchinson-Gilford progeria syndrome are a typical example; the disease is caused by a mutation in the LMNA gene that encodes lamin A, an essential scaffold protein for the maintenance of normal cell nucleus shape and function. Cells with the genetic mutation are more likely to die prematurely. Therefore, children with progeria often die early from heart attacks caused by cardiovascular disease, and usually only have a lifespan of about 15 years.

Environmental factors also play an important role; for example, there are studies that provide evidence that over-nutrition or diets rich in energy may accelerate cellular and organismal ageing, while dietary or energy restriction may have beneficial effects on cardiovascular function and metabolic phenotypes. In many animal models, this approach has even been shown to extend lifespan.

How could targeting arginase-II (Arg-II) decelerate vascular ageing and the development of associated diseases?

Our research over recent years has demonstrated that Arg-II expression and activity are not only positively associated with cellular senescence, organism ageing, cardiovascular disease and obesity, but also play a causative role in this context. Although the underlying mechanisms are still under investigation, we have been able to show that inflammation, oxidative stress and endothelial dysfunction are involved.

So far, there are no specific Arg-II inhibitors available. Some inhibitors used in various research works are not isoform-specific, ie. they also inhibit liver Arg-I, and so would cause severe health problems. Hence, specific Arg-II inhibitors must be developed. These inhibitors are expected to reduce inflammation and oxidative stress, and improve vascular endothelial function, leading to the deceleration of ageing and its associated complications.

It is also important to note that Arg-II exerts pleiotropic harmful effects on the vasculature, which are not necessarily related to L-arginine metabolism. Therefore, drugs that are able to specifically inhibit Arg-II protein expression are expected to be more beneficial than drugs that inhibit enzymatic activity alone.

Where do you see your research heading in the near future?

The main aim of my research group at present is to understand what causes Arg-II up-regulation during the ageing process and elucidate how this is regulated. In addition, we would like to explore the detailed underlying mechanisms involved in how Arg-II activates several signalling pathways that lead to organism ageing and organ failure. Our long-term goal is to translate our findings to the clinic and develop specific Arg-II inhibitors. This warrants continual collaboration with other research groups.
ACROSS THE WORLD, people are living longer than ever before; according to World Health Organization statistics, average global life expectancy at birth increased by six years between 1990 and 2013, rising from 65 to 71 years. Furthermore, a growing proportion of people are surviving into advanced old age, with many individuals living into their eighties, nineties and even past 100.

Increased longevity, however, comes at a cost, not just in terms of everyday ageing but also in increased risk of age-associated diseases such as cardiovascular disease and type 2 diabetes. Incidence of such conditions is on the rise – a trend further compounded by an increase in other risk factors such as obesity. As a result of this demographic shift, researchers are focusing their attention on devising novel ways to respond to the major public health challenges ahead.

SPOTLIGHT ON ARGINASE

One such researcher is Dr Zhihong Yang, Leader of the Laboratory of Cardiovascular and Ageing Research within the Department of Medicine and Division of Physiology at the University of Fribourg, Switzerland. Yang’s team is investigating the role of vascular dysfunction in age and age-associated conditions, with a particular focus on its relationship with oxidative stress, inflammation and accelerated cell senescence. To explore such aspects, the Fribourg researchers employ a combination of complementary pharmacological and genetic approaches.

In recent years, the Laboratory of Cardiovascular and Ageing Research has conducted cutting-edge studies aimed at elucidating the role of arginase in vascular ageing and associated diseases. Arginase is an organic enzyme that comes in two isoforms – arginase-I (Arg-I) and arginase-II (Arg-II) – which were first identified in the 1980s and 1990s, respectively. Although both isoforms exist in the human body, Arg-I is expressed in the liver, where it detoxifies ammonia through the urea cycle, while Arg-II is inducible in numerous other cells, including vascular and inflammatory ones. However, given the relatively recent identification of these two isoforms, there is still much that remains unknown in terms of their various functions in the body.

A CAUSATIVE ROLE

It was this dearth of information that first sparked Yang and his team’s interest in arginase over a decade ago. Initially, the scientists realised that arginase plays a vital role in the hydrolysis of L-arginine – a semi-essential amino acid utilised by vascular endothelial cells to produce the vasoprotective molecule nitric oxide via endothelial nitric oxide synthase (eNOS). This led us to hypothesise that arginase may play a role in impairing eNOS function in vascular endothelial cells and, in turn, may contribute to the pathogenesis of atherosclerosis,” Yang recalls. Their investigations not only successfully demonstrated this effect, but also revealed that Arg-II played a particularly prominent role in the process.

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More recently, the researchers have turned their attention to Arg-II’s relationship to macrophage inflammatory functions; until this time, it had been hypothesised – but not proven – that Arg-II performed an anti-inflammatory role. “We realised that no study provided convincing evidence to demonstrate a role of Arg-II in macrophage inflammatory functions,” Yang explains. This realisation resulted in a 2012 systematic investigation, in which the team set out to investigate the signalling transduction pathways that regulate Arg-II expression and activity in...
endothelial cells and macrophages in models of atherosclerosis, type 2 diabetes and age-associated vascular dysfunction. This study produced a number of significant findings, including the insights that crosstalk between Arg-II and the S6K1 protein promotes eNOS-uncoupling and thus leads to endothelial inflammation and ageing, and that Arg-II promotes macrophage inflammatory responses and mitochondrial reactive oxygen species formation, and so contributes to type 2 diabetes and atherogenesis. This study was also the first to definitively demonstrate that Arg-II plays a causal role in macrophage pro-inflammatory responses. “This suggests that Arg-I and Arg-II have different functions in macrophage inflammatory responses or phenotype regulation,” elaborates Yang.

**FURTHER INVESTIGATIONS**

In light of these important discoveries, the Laboratory has set about extending understanding in this area by exploring the role played by Arg-II in vascular cell dysfunction, with a particular focus on senescence, apoptosis and the impairment of autophagy, a cellular self-repairing mechanism. One study saw the researchers using human umbilical vein smooth muscle cells (SMCs) to investigate whether Arg-II can exert certain biological effects independently of eNOS. “We showed that Arg-II not only accelerates SMC senescence/ death, but also promotes SMC proliferation,” reveals Yang. “The latter effect may contribute to vascular wall thickening, lumen narrowing and stiffness – phenomena observed in older people that lead to hypertension.”

Another recent study has looked at the role of Arg-II in the modulation of endothelial autophagy and examined the potential underlying mechanisms involved. The researchers were able to demonstrate that Arg-II pleiotropically impairs endothelial autophagy independently of L-arginine ureahydrolase activity via the simultaneous activation of S6K1 and inhibition of the enzyme AMPK. “This is one of our most exciting findings to date,” Yang enthuses. “This effect involves pathways that link to cellular ageing and cell death, as well as impairment of autophagy. As such, we are now interested in exploring the underlying mechanisms of the pleiotropic functions of Arg-II.”

A fuller understanding of how Arg-II contributes to vascular ageing and the onset of associated diseases could lead to the development of inhibitors specific to the Arg-II isoform. If Arg-II can be successfully and safely inhibited, then this paves the way for the development of novel therapeutics aimed at improving vascular health with age.

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**IMPACT OF LONG-TERM EXPOSURE TO HIGH AMINO ACID DIET ON HEALTHY AGEING**

**OBJECTIVE**

To use integrative research approaches ranging from genetic modifications, signal transductions and cellular functional analysis to whole body in vivo pathological experimental models to investigate ageing and age-related diseases.

**KEY COLLABORATORS**

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**DR ZHIHONG YANG** studied medicine at Wuhan Tongji-Medical University, China, in 1987. From 1988 to 1991, he completed his postgraduate cardiovascular research training at the University Hospital Basel, Switzerland. He became a research assistant, then senior research associate, in cardiology at University Hospital Inselspital, Bern, and from 1997 held the same position within the Institute of Physiology at the University of Zurich, Switzerland. In 1999, Yang Habilitated in Cardiovascular Physiology at the University of Zurich. He became Associate Professor in 2000 within the Division of Physiology’s Department of Medicine at the University of Fribourg, Switzerland. Since then, he has been actively engaged in education programmes for medical and biomedical science students, and continues his research on atherosclerosis, metabolic cardiovascular stress and ageing-associated cardiovascular dysfunctions.