Preventing Vascular Ageing as a **Means of Life Extension**

Dr Yu Wang

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Dr. Yu Wang is a cardiovascular medicine research scientist interested in the ageing processes occurring in mammals. Her research has been focused on understanding how the blood vessels age, and specifically on the role played by SIRT1 protein, a longevity regulator.

To aid our readers better understand your work, please tell us how your research background led to your interest in vascular ageing?

It was my strong curiosity of research- and technology-based discovery led to my current interest in vascular ageing. Eighteen years ago I started a research project in the University of Auckland focusing on metabolic hormones and their potential in the treatment of type two diabetes. I identified a novel phosphoprotein, P20, involved in the signalling pathways of two important metabolic hormones, and a glycosylated adiponectin, which we identified as an important hormonal factor for regulating lipid homeostasis. Although we did not discover a drug so far, the experience of these pioneering results convinced me to follow my own true and reproducible results.

The results obtained at the University of Hong Kong set the foundation for my current interest in vascular ageing. They showed the endothelial dysfunction occurs much earlier than those of the metabolic defects in various animal models with metabolic syndrome. For example, vascular insulin resistance can be detected as early as at three weeks of high fat diet whereas metabolic insulin resistance appears at around two month of the same dietary treatment. This indicated that vascular abnormality may represent a major culprit for many ageing-related diseases. Thus, it is crucial to understand the fundamental etiopathogenesis for early vascular ageing.

The role and functioning of the SIRT1 protein are central to your research. Why this specific enzyme and why now – what role does SIRT1 play in current biomedical research?

SIRT1 (Sirtuin 1) is a longevity regulator and plays a unique role in the prevention of endothelial senescence and vascular ageing. As an enzyme, its activity can be modulated by pharmacological approaches. SIRT1 differs from other sirtuins in that it contains extra-long NH2- and COOH-terminal domains that are dynamically regulated by posttranslational modifications, which affects the enzyme activity. Identification of the signalling pathways responsible for modifying the termini will uncover more specific biological process for targeted therapy against early vascular ageing. For example, the CDK5 as an upstream kinase of SIRT1 phosphorylation may be a potential drug target, if a detailed functional relevance of this regulation within the vasculature wall becomes available.

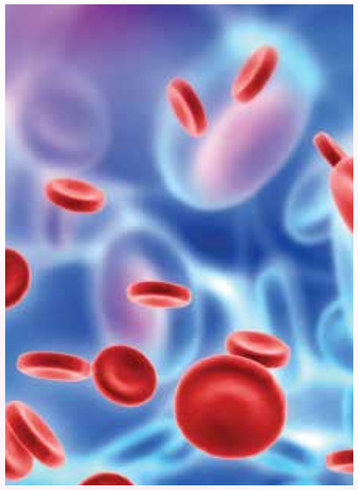
Does SIRT1 hold any promise from a therapeutic standpoint? How might a potential SIRT1-based treatment be implemented?

As mentioned above, SIRT1 has already been identified as a promising anti-ageing candidate. However, more investigations are needed to understand its signalling and functional mechanisms, in order to identify drugs that can modulate a specific signalling pathway within a fully-defined tissue/cell type for modulating SIRT1 activity.

How do you expect this study to affect your future work? Might it contribute to healthcare, society and/or policy?

Life expectancy has been creeping upwards in most countries for many years. The portion of people aged over 80 years is growing faster than any other age groups and will exceed the number of young (under the age of 15) people by 2050 for the first time in history. Population ageing will pose a great challenge to global healthcare system in 21th century, as ageing-associated organ dysfunctions are the major culprits for the world's leading causes of death. To develop therapeutics for preventing early vascular ageing will not only help to reduce the healthcare burden for chronic diseases but also increase the workable population beyond the current retirement age.

Have you worked with any other researchers for this study? If so, how did they contribute?



I feel very lucky to have met Prof Paul M Vanhoutte, whose passion in vascular biology has greatly inspired me. In addition, our achievement in the field should be credited to the friendly and stimulating research environment in the Department of Pharmacology and Pharmacy, the University of Hong Kong, and the hard working students and research fellows.

Will you extend this research further? Which directions are you interested in exploring further and why?

Our research has been expanding and extending from endothelial senescence to endothelial dysfunction, atherosclerosis and vascular ageing. Since the actions of SIRT1 are tissue- and organ-specific, our goal is to focus on the endothelial SIRT1 and elucidate endothelial-selective pathways for targeted drug discovery and development. During the next few years, we will also concentrate on the molecular events and signalling mechanisms underlying early vascular ageing.

Promising prospects for novel anti-ageing treatments

Ageing and especially anti-ageing treatments are topics that have fascinated mankind from very early on. Current anti-ageing research, such as Dr. Yu Wang's work on vascular ageing prevention offers new perspectives on curing illnesses associated with old age and hopes of slowing down the aging process.

LIFE EXTENSION BY CALORIC RESTRICTION

Researchers have shown as early as 1930's that a low calorie intake (caloric restriction, CR) without malnutrition can as much as double laboratory rats' life spans. Since that seminal experiment the hypothesis that CR can extend life has been tested on a number of species. The results showed that a caloric restrictive diet can results in an increase (sometimes by as much as 10-fold) in the lifespan of many, but not all species.

Despite the mixed results on interspecies effects and the relatively few studies on primates (two randomised control studies on rhesus monkeys and one study on human volunteers started in the 1980's; and two studies on humans started in 2007 and 2010, respectively), life extension has been a topic of interest to sufficiently many people that CR has been quick to enter the pop culture. Of those who have already subjected themselves to CR in the hopes of increased longevity or improved health, staying on the diet has proved challenging. In reality, the long-term health effects of moderate CR with sufficient nutrients are as of yet unknown in humans.

Identification of the signalling pathways responsible for modifying the unique regions of SIRT1 will uncover more specific biological process for targeted therapy against early vascular ageing.

ANTI-AGEING: A GENETIC APPROACH

In parallel with research efforts such as the primate and human studies mentioned above, which measure the effects of CR, a significant body of work exists that attempts to understand why CR leads – at least in some cases – to greater longevity and/or fewer or less severe illnesses associated with the old age. A genetic approach led to the discovery of the sirtuins in early 1980's. Sirtuins are a family of NAD+-dependent protein deacetylases that exert multiple cellular functions. Sir2 (Silent information regulator 2), was the first gene discovered in this family in the budding yeast, but its role in caloric restriction-dependent lifespan extension was not known until 2000, when it was referred to as the "longevity protein Sir 2". Sirtuins are highly conserved during the evolution from bacteria to humans and genetically modified yeast cells overexpressing Sir2 showed 30 per cent longer lifespan, while those lacking the Sir2 gene showed 50 per cent reduction in lifespan. Similar effects of Sir2 on lifespan were subsequently observed in other lower organisms.

Sirtuins are hypothesised to play a key role in an organism's response to stresses (such as heat or starvation) and to be responsible for the lifespan-extending effects of calorie restriction. In mammals, the family is represented by seven members named SIRT1-7, which share the catalytic domain with Sir2. SIRT1 is the mammalian orthologue most highly related to Sir2 and Dr. Wang's research programme focuses on understanding the role played by SIRT1 in mammals.

MAMMALIAN SIRTUINS

Sir2 plays a direct role in anti-aging in species as varied as yeast, worm and fruit flies. In higher organisms SIRT1 works by a more complex mechanism and appears to operate in an indirect manner, targeting the cellular energy metabolism in ways that benefit normal physiology. To that end, an energy-sensor network model has been put forward recently, which proposes that SIRT1 adjusts cellular responses to the energetic state of the cell. By deacetylating transcription factors, cofactors, and histones, SIRT1 has been shown to promote resistance to metabolic, hypoxic, and genotoxic stress, thereby controlling cell metabolism, survival, proliferation, and cell fate. SIRT1 achieves this formidable task by not being specifically localised in the cell, but instead shuttling between the cytoplasm and the nucleus.

More recent studies highlighted important homeostatic functions of SIRT1 in the vascular endothelium, where it modulates vascular growth, shape and function. Prof. Paul M Vanhoutte, a medical doctor specialising in vascular biology has played a significant role in Dr. Wang's research efforts to understand SIRT1's role specifically in vascular ageing. By studying the thin layer of cells on the interior surface of blood vessels, which separate the circulating blood from the rest of the vessel wall (the endothelium), Dr. Wang observed that endothelial dysfunction occurs much earlier than those of the metabolic defects in various animal models with metabolic syndrome. Vascular abnormality may represent a major culprit for many ageing-related diseases. Dr. Wang and Prof. Vanhoutte's recent work suggests that in aged arteries, SIRT1 expression and activity is blunted, which contributes to the development of atherosclerosis and abnormal vascular responses. A recent study suggests that cyclin-dependent kinase 5 (CDK5) is responsible for the phosphorylation of SIRT1, which blocks the anti-senescence activity of SIRT1 and plays a critical role in the loss-of-SIRT1 function during vascular ageing. Thus, by inhibiting CDK5, SIRT1 function can be improved, in turn preventing the development of atherosclerosis and slowing down the process of vascular ageing.

HEALTHCARE APPLICATIONS

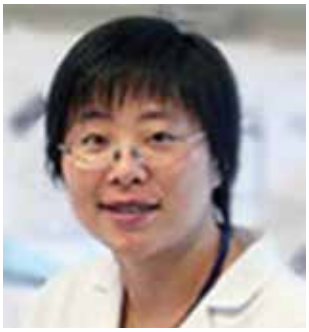
Life expectancy has been creeping upwards in most countries for many years. The portion of people aged over 80 years is growing faster than any other age groups and will exceed the number of young (under the age of 15) people by 2050 for the first time in history. Population ageing will pose a great challenge to global healthcare system in 21th century, as ageing-associated organ dysfunctions are the major culprits for the world's leading causes of death. To develop therapeutics for preventing early vascular ageing will not only help to reduce the healthcare burden for chronic diseases but also increase the workable population beyond the current retirement age.

As mentioned above, SIRT1 has already been identified as a promising anti-ageing candidate. However, more investigations are needed to understand its signalling and functional mechanisms, in order to identify drugs that can modulate a specific signalling pathway within a fully-defined tissue/cell type for modulating SIRT1 activity.

As an enzyme, SIRT1's activity can be modulated by pharmacological approaches, especially in endothelial cells - the direct contact with the blood stream. Unlike the other members of sirtuins, SIRT1 contains extra-long NH2- and COOH-terminal domains that are dynamically regulated by posttranslational modifications, leading to enhanced or decreased enzyme activity. Thus, identification of the signalling pathways responsible for modifying these unique regions of the protein will uncover more specific biological process for targeted therapy against early vascular ageing. The identification of CDK5 as one of the upstream kinases of SIRT1 has uncovered an important regulatory pathway and provides a new strategy for combating vascular ageing to inhibit hyperphosphorylation of SIRT1 by antagonising CDK5 activity. This, and other approaches, may effectively slow down the vascular ageing process in line with the pace of chronological ageing, in turn reducing the risks of ageing-induced cardiovascular events.

Dr. Wang's research has been expanding from endothelial senescence to endothelial dysfunction, atherosclerosis and vascular ageing. During the next few years, she is planning to concentrate on elucidating the molecular events and signalling mechanisms underlying early vascular ageing, especially how these contribute to the alterations of individual components within the arterial wall.

Researcher Profile



Dr. Yu Wang
Associate Professor
Department of Pharmacology & Pharmacy
The University of Hong Kong

Dr. Yu Wang is a researcher in the Department of Pharmacology and Pharmacy at the University of Hong Kong. Her research interests have been led by various abnormalities within the field of cardiometabolic syndrome, since the initial encounter with biological research at the University of Auckland about eighteen years ago. Currently she is primarily working on vascular ageing and specifically the mechanisms of action of SIRT1, a protein deacetylase involved in caloric restriction-dependent life extension. While not in the laboratory, Dr. Wang enjoys spending time with her husband and three children, as she places equal importance of having a happy family and a successful career.

CONTACT

E: yuwanghk@hku.hk
T: +852 3917 6864
W: http://www.pharma.hku.hk/pharma/staffweb/DrYuWang/index.php

KEY COLLABORATORS

Prof. Paul M Vanhoutte, the University of Hong KongProf. Garth JS Cooper, University of Manchester
Dr. Alok Mitra, The University of Auckland
Prof. Jo De Mey, University of Southern Denmark
Dr. Gary Sweeney, York University
Dr. Weiping Han, A*STAR , Singapore

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