JOINT NEWS RELEASE

Singapore, 3 Sep 2021

Singapore researchers develop novel 3D model to study vascular diseases

A Singapore team of scientists and clinicians from **Nanyang Technological University, Singapore (NTU Singapore)** and **Tan Tock Seng Hospital (TTSH),** have developed a three-dimensional (3D) model of the human artery blood vessel wall.

Called an "arterial wall-on-a-chip", it will help researchers study atherosclerosis, a condition in which cholesterol and inflammatory cells form a plaque on blood vessel walls that results in the vessels narrowing and constricting blood flow, leading to cardiovascular diseases.

Cardiovascular diseases account for some 32 per cent of the deaths worldwide[1], claiming some 17.9 million lives annually. In Singapore, about 6,990 deaths or about 1/3 of all deaths in 2020 were due to heart disease or stroke.

This 3D model resembles a sandwich. It comprises a 3D culture of vascular smooth muscle cells, a soft gel layer in the middle, and a layer of endothelial cells that line the inside of the heart and blood vessels. This last layer controls the exchange of molecules between the bloodstream and the surrounding tissues.

The team used this new microfluidic chip, which mimics the cross-section of an arterial wall, to study the effects of oxidative stress on blood vessels, which is usually caused by conditions such as high cholesterol (hyperlipidemia) and inflammation.

Oxidative stress occurs in the human body when there is an imbalance of free radicals and antioxidants. Free radicals are produced during the body's natural metabolic processes, while antioxidants protect cells and tissues by neutralising these free radicals.

[1] Cardiovascular diseases (CVDs). (2021, June 11). WHO. https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)#:%7E:text=Key%20facts,to%20heart%20attack%20and%20stroke.

The study, published in the journal *Lab on a Chip* in June, found that as oxidative stress increase, smooth muscle cells which are found in the middle layer of arteries move inwards, causing inflammation on the endothelial layer on the interior of the artery (See
Figure 1 - Structure of an Artery Wall).

There was also more build-up of "bad cholesterol" or low-density lipoprotein (LDL) cholesterol, and immune cells (white blood cells) on the endothelial layer, which contribute towards blood vessel hardening and plaque growth during atherosclerosis.

This was the first time the above effects have been observed in 3D, since previous studies on atherosclerosis have been carried out using animal models, or two-dimensional (2D) cell cultures, which do not fully reveal the interactions between smooth muscle cells and the endothelial layer.

The discovery was made by an interdisciplinary team jointly led by **Assistant Professor Hou Han Wei** from the **NTU School of Mechanical and Aerospace Engineering**, and **Senior Consultant, Endocrinology, TTSH, Associate Professor Rinkoo Dalan,** who is a joint faculty with the **Lee Kong Chian School of Medicine**, in collaboration with **Assistant Professor Dalton Tay** from the **NTU School of Materials Science and Engineering.**

Senior author of the study, **Asst Prof Hou**, also a faculty member in **NTU's Lee Kong Chian School of Medicine**, said: "Our new 'wall-on-a-chip' model could help clinicians better understand the fundamental biology and conditions of vascular dysfunction when atherosclerosis starts, and the different processes involved in its progression, so that new strategies for early intervention of atherosclerosis can be developed."

As part of the study, the team tested two compounds, Vitamin D and metformin (a common diabetes medication) and showed that they can help to prevent smooth muscle cell migration and immune cell adherence, the two key processes involved in atherosclerosis.

In the future, new drug compounds and molecules can also be tested using the arterial wall-on-a-chip to assess their effectiveness in preventing the effects of oxidative stress, or perhaps to reverse migration of the smooth muscle cells.

Assoc Prof Dalan said that out of all the deaths caused by cardiovascular diseases, 58 per cent had occurred in Asia[3]: "Despite significant advances in treatment, the mortality and morbidity associated with atherosclerosis remain high. There is an unmet need to understand the disease mechanisms and processes of atherosclerosis in a

[3] Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. (2020, December 22). ScienceDirect. https://www.sciencedirect.com/science/article/pii/S0735109720377755

typical patient who is suffering from multiple diseases, such as diabetes and high blood pressure. “The development of this “arterial wall-on-a-chip” enables us to study the process of atherosclerosis under various conditions as well as the possible impact of therapeutics and drug combinations, which will have wide applications.”

Professor Derek John Hausenloy, Cardiovascular & Metabolic Disorders Programme, Duke-NUS Medical School and the **Director of the National Heart Research Institute Singapore,** gave an independent comment on the research findings: “Cardiovascular diseases are the leading causes of death and disability in Singapore and worldwide. These include cerebrovascular, coronary arterial and peripheral arterial disease, the major cause of which is atherosclerosis. The ability to model atherosclerosis using this novel human arterial wall-on-a-chip will enable the discovery and validation of novel treatment targets for preventing atheroma (plaque) formation and improving health outcome in patients with these conditions.”

Finding the optimal hydrogel (or extracellular matrix) components was key in setting up this 3D co-culture model which contains multiple types of cells, so that both the vascular smooth muscle cells and endothelial cells are retained in a “healthy” state that accurately represents the human arterial wall.

Asst Prof Tay, also a faculty at **School of Biological Sciences** and an expert in developing hydrogels, said: “This research underscores the importance of an interdisciplinary approach to tackle complex diseases. By coupling the different biological cells with the optimal cell culture materials, it is now possible to recreate and mimic the actual conditions and states in a blood vessel that are caused by atherosclerosis.

“This is a positive step in the development of *in vitro* pre-clinical platforms that may gradually replace animal testing for a better understanding of diseases and drug testing.”

The team now plans to conduct more experiments to further improve the modelling using their new chip and to use it to study other vascular diseases, in addition to atherosclerosis at varying stages of development.

This innovation is aligned with the **NTU 2025 Strategic Plan,** where responding to the needs and challenges of healthy living and aging is one of the four humanity’s grand challenges the University aims to address.

END

Note to Editors:

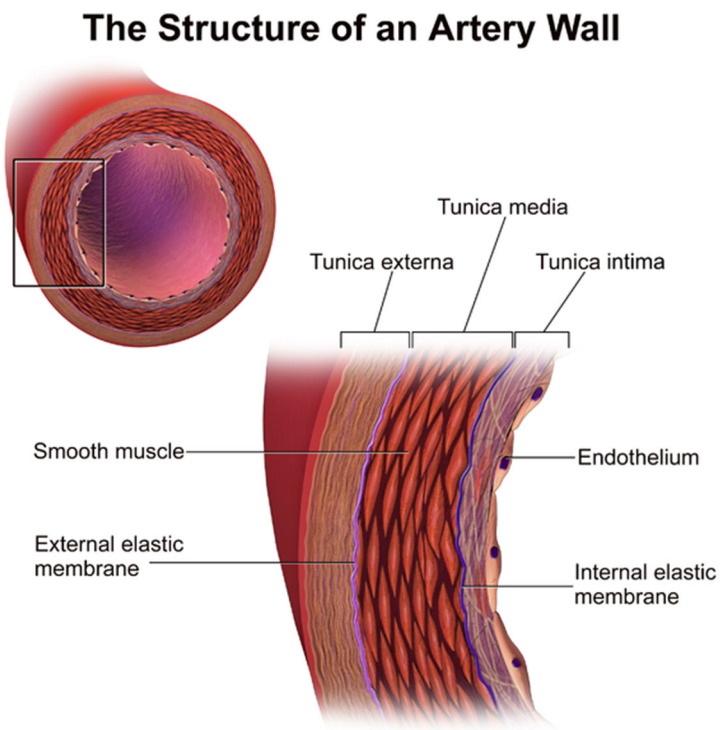

Figure 1 - Structure of an Artery Wall
Credit: Blausen.com staff (2014). "Medical gallery of Blausen Medical 2014". WikiJournal of Medicine 1 (2). DOI:10.15347/wjm/2014.010. ISSN 2002-4436.

***Paper titled**: "A novel human arterial wall-on-a-chip to study endothelial inflammation and vascular smooth muscle cell migration in early atherosclerosis", published in Royal Society's Lab on a Chip, Issue 12, 21 June 2021.*
https://doi.org/10.1039/D1LC00131K

Media contact:

Lester Kok
Assistant Director
Corporate Communications Office
Nanyang Technological University
Email: lesterkok@ntu.edu.sg

Isabella Wong
Communications Executive
Tan Tock Seng Hospital
Email: Hsin_Isabella_Wong@ttsh.com.sg

About Nanyang Technological University, Singapore

A research-intensive public university, Nanyang Technological University, Singapore (NTU Singapore) has 33,000 undergraduate and postgraduate students in the Engineering, Business, Science, Humanities, Arts, & Social Sciences, and Graduate colleges. It also has a medical school, the Lee Kong Chian School of Medicine, established jointly with Imperial College London.

NTU is also home to world-renowned autonomous institutes – the National Institute of Education, S Rajaratnam School of International Studies, Earth Observatory of Singapore, and Singapore Centre for Environmental Life Sciences Engineering – and various leading research centres such as the Nanyang Environment & Water Research Institute (NEWRI) and Energy Research Institute @ NTU (ERI@N).

Ranked amongst the world's top universities by QS, NTU has also been named the world's top young university for the last seven years. The University's main campus is frequently listed among the Top 15 most beautiful university campuses in the world and it has 57 Green Mark-certified (equivalent to LEED-certified) building projects, of which 95% are certified Green Mark Platinum. Apart from its main campus, NTU also has a campus in Singapore's healthcare district.

Under the NTU Smart Campus vision, the University harnesses the power of digital technology and tech-enabled solutions to support better learning and living experiences, the discovery of new knowledge, and the sustainability of resources.

For more information, visit www.ntu.edu.sg