

The future of lipidomics

In recent years, lipidomics has emerged as a new scientific discipline. **Professor Markus Wenk** describes the importance of this field in terms of developing therapeutic targets for disease



To begin, can you explain what attracted you to the emerging field of lipidomics?

Lipids have been neglected for a long time. The discovery of the DNA structure drew all attention to nucleic acids and later to proteins. Now it is becoming increasingly clear that aberrant lipid metabolism is linked to many human diseases. However, there are not many modern technologies available for isolation, detection, characterisation and quantification of lipids. These two concomitant developments, ie. technological advances over the past 20 years and renewed interest in lipid metabolism, have led to the emerging field of lipidomics. Our main interest is in integrating novel technologies with applications in this area.

Has there been a visible progression of research conducted in this area alongside the advancement of technology?

Mass spectrometry has tremendously advanced the field of lipidomic research. It is now possible to determine the

composition of complex lipid mixtures from a limited amount of starting material (eg. those found in an extract from a drop of blood or 100,000 cells). This was not possible 25 years ago. More recently, new approaches at the interface of chemistry and biology (chemical biology) have made it possible to investigate lipid metabolism in living cells. Lastly, we are now seeing the first examples of integrated 'omics', ie. combinations of genomics, proteomics and lipidomics.

What are some of the wide range of implications of lipids in biological systems?

Lipids are one of the four main classes of biomolecules in living matter (in addition to nucleic acids, amino acids and carbohydrates). They occur in all living organisms and are major components of biological membranes. Their structural roles in membranes as well as their metabolic functions in energy homeostasis are well described, although many open questions remain regarding the chemical diversity of lipids and the regulation of metabolism. Furthermore, lipids are now also recognised for their important signalling functions at the cellular and organismal levels. For example, inflammation at the molecular level is tightly linked to lipid metabolism and has been therapeutically targeted with some of the most widely used medications (aspirin, other cyclooxygenase inhibitors, etc.).

Can you explain the main aims of the Singapore Lipidomics Incubator (SLING), and outline the ways in which the centre will aid collaboration between parties involved in lipidomics?

SLING is a major global magnet for collaborating parties in lipidomics – from

academia and industry – delivering new technologies and intellectual capital. Our centre offers cutting-edge facilities and a diverse base of investigators and students, anchored at the National University of Singapore (see p6) a leading global university in Asia.

As Head of the centre, what are your main goals over the next few years?

I have to coordinate activities within the programme and interactions with other entities. We are entering into major collaborations within the Life Sciences Institute (LSI) and with clinical and applied research groups at local hospitals such as the National University Health System (NUHS), the Singapore Eye Research Institute (SERI) and the Agency for Science, Technology and Research (A*STAR; see p13) community of research institutes which are all in relatively close physical proximity.

How do you see lipidomics developing in the future and how will your research contribute towards this?

The field will see a dramatic expansion due to our rapidly increasing realisation that lipids are relevant to so many different functions in biological systems. The main applications will likely be focused on biomedical and environmental sciences, thus life sciences in general. At the moment, a lot of lipidomics research remains concentrated in a relatively small (albeit rapidly expanding) base of laboratories and centres. Commercial products would make lipid isolation and detection available for a larger and more diverse community. These products would, for example, include kits and devices for easy isolation and analysis of lipids that are of particular biological interest. Our aim is to facilitate this development.

Learning about lipidomics

Lipids are present in the cells of all living organisms, yet their huge number and diversity has made them difficult to study. A Singaporean group – the [Singapore Lipidomics Incubator](#) – is driving lipidomics research forward, shedding light on the nature of these biomolecules and their role in metabolism along the way

LIPIDS ARE THE 'fats and oils' that make up cell membranes and are involved in homeostasis and signalling in cells and tissues. Despite being one of the major classes of biomolecules in living organisms, they have received relatively little attention from scientists to date. This is mainly because they have been overshadowed by the study of nucleic acids and proteins, but also due to the difficulty in isolating and analysing them. With the advancement of technology, particularly methods of mass spectrometry, the field of lipidomics has emerged. Here, the systems-level analysis of lipids and the pathways and networks in biological systems which they are involved in are beginning to be explored.

Lipids are generated and metabolised by enzymes, rather than being coded for by DNA, thus their presence and functionality are greatly influenced by the environment of their biological system. Dysfunctionality of lipids and lipid metabolism are linked to a number of diseases including cancer, diabetes, neurodegenerative disorder and infectious diseases. Thus, there is an increased interest in lipidomics as researchers are seeking to produce biomarkers and interventional drugs.

Several classes of lipids are biochemically relevant: the amphiphilic lipids that make up membranes, more polar signalling lipids and extremely non-polar molecules such as sterol-esters and triglycerides that are stored in lipid droplets within cells. However, the number of distinct chemical entities is yet to be defined, with estimates ranging from 10,000-100,000, demonstrating a staggering diversity. Due to

this, it is not currently possible to measure the lipidome (the complete lipid profile) of a cell or tissue in a single experiment. Methods to more accurately isolate and characterise lipids are currently under development.

LIPID ANALYSIS

Professor Markus Wenk of the Yong Loo Lin School of Medicine at the National University of Singapore is pushing the boundaries of lipid research through collaborative initiatives. He has a number of research goals that he hopes will develop the field of lipidomics and its possible applications. Wenk uses targeted and non-targeted approaches based on chromatography and mass spectrometry to conduct comparative studies of complex lipid mixtures found in cells and tissues. This could potentially reveal lipid biomarkers, as the presence of lipids in membranes or as signalling molecules is reflective of the physiological state of an organism at a given time.

Such lipid analysis generally involves the application of mass spectrometry via soft ionisation techniques. This has been aided by the commercial availability of deuterated pure synthetic lipid standards that are used to quantify ion responses in a given experiment. The most important advancement has been the development of high sensitivity and high mass resolution mass spectrometers, which have enabled the detailed analysis of these lipids in a given sample. However, it is still difficult to detect lipid species that are in very low abundance. High mass resolution has enabled

previously uncharacterised lipids to be identified and those with similar mass or chemical structure to be discriminated. However, despite advances in mass spectrometry that have allowed these developments in lipidomics to occur, there are several analytical challenges that cannot be overcome by this technique alone.

DEVELOPING TECHNIQUES

Wenk makes continuous efforts to develop spectrometric methods for use in lipidomics, and has the view that analytical techniques such as inductively coupled plasma (ICP) mass spectrometry and coherent anti-Stokes Raman scattering (CARS) microscopy could facilitate the identification and characterisation of lipids. However, one of the main challenges in lipidomics is handling the large amount of data from mass spectrometric and chromatographic experiments. There are large computational and bioinformatic demands both during data acquisition and processing.

Some commercial software packages are now available to support these functions, and Wenk believes that building databases of lipids will also aid the future development of lipidomics. Most recently, he has been focusing on the development of new materials and devices for the capture and separation of lipids. These developments may enable lipids of low abundance to be identified more easily. In addition to these initiatives, Wenk and his collaborators have developed approaches that enable the detection of lipids in cells. These are based on chemical biology and antibody technologies. It is hoped that

INTELLIGENCE

LIPIDOMICS PROGRAMME

OBJECTIVES

- Concept, design and development of next-generation integrated workflows ('wet' and 'dry', ie. experimental and computational) for characterisation of lipidomes ('model organisms to man')
- Fundamental understanding of natural variation at the level of lipid metabolism (integration of lipid biochemistry with epidemiology and genetic variation)

KEY PARTNERS

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ROFESSOR MARKUS WENK has been interested in membrane lipids, their structure and function since his undergraduate years at the Biozentrum of the University of Basel. More recently, he established the Singapore Lipidomics Incubator (SLING), an interdisciplinary programme dedicated to innovation, education and partnership in lipidomics research at the National University of Singapore (NUS). Wenk is currently Associate Professor of Biochemistry at NUS, Director of SLING and Privatdozent at the University of Basel. He is also the founder and organiser of the biennial International Singapore Lipid Symposium and an Executive Editor of *Progress in Lipid Research*.

through this the structure and function of lipids in particular locations within a cell can be determined, as when whole cell extracts are used the spatial information is lost. There is also progress in integrating lipidomics with other 'omics' approaches: "The research efforts of my own group will focus on new conceptual approaches for integration of lipidomics with genomics," Wenk reveals. "Ultimately, we wish to understand how genetic variation relates to variation of lipid metabolites at the levels of individuals and populations."

recently, several of these collaborations have started to align along focal themes. For example, initiated within SystemsX.ch, the Swiss Tropical and Public Health Institute in Basel is now spearheading lipidomics of host-pathogen interactions. There are also projects with leading measurement companies dedicated to the development of novel integrated workflows for lipidomics.

SLING

In order to further develop the studies of lipidomics and to provide a platform for international collaboration and research, Wenk has established the Singapore Lipidomics Incubator (SLING), the first centralised lipidomics programme for collaborative research in the world. SLING's scientific aims are to develop next-generation workflows for characterisation of lipidomes and to determine and understand natural variation of lipids in biological systems: "In essence, we would like SLING to be a 'thought leader' for lipidomics at a global level," summarises Wenk. The group emerged from the development of a five-year competitive research programme 'Lipidomics: novel tools and applications' that was funded by the Singapore National Research Foundation.

SLING organises several events each year to foster interdisciplinary research. The most important event in the calendar is the International Singapore Lipid Symposium (ISLS), a biennial research meeting that attracts researchers from different disciplines. ISLS is now established as a key event in the field and in the Asia-Pacific region, and it has gained global recognition as the place to keep up to date with lipid and lipidomic research.

It is an exciting time for lipidomics. SLING is likely to facilitate collaboration between research institutes on a global scale and ensure that this field continues to advance. It is hoped that the integration of lipidomics with genomics, proteomics and chemical biology through interdisciplinary collaborations will develop our understanding of biological systems as a whole.

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LIPIDPROFILES

Wenk's research group – LipidProfiles – aims to drive technology and lipid biology research forward. His team applies their knowledge to applications in medicine and environmental sciences. Unsurprisingly for a group with such wide-ranging aims, LipidProfiles collaborates with a number of laboratories worldwide: "Collaboration is key to our research," emphasises Wenk. "We do almost everything in partnership."

An example of this comes from their development of novel mass spectrometry techniques designed to support applications in basic research of model organisms such as baker's yeast or the fruit fly. As individual laboratories in Singapore, the Asia-Pacific region and eventually worldwide who study such model organisms began to become interested in these techniques, many collaborations blossomed to adapt their techniques in order to answer specific biology questions. More

