
Babraham
Institute

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(Left in 2018)

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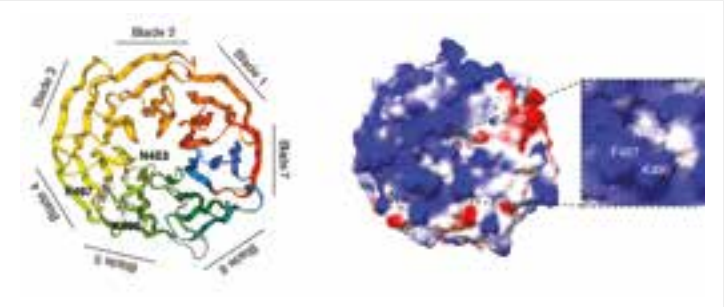
Understanding autophagy and cellular recycling



Ribbon model of the top face of Atg16L1 WD domain, with critical residues in ball and stick and a surface model coloured to electrostatic potential (blue positive, red negative).

Cells need to be able to break down and recycle parts of themselves, a process called autophagy, so they can stay healthy. Disruption of this process is associated with many age-related e ects, including cancer and neurodegeneration. Our research explores the molecular mechanisms underlying autophagy and several similar pathways to understand their roles in health and disease.

Current Aims

Our goal is to understand the upstream regulation and downstream consequences of a ‘non-canonical’ autophagy pathway, which utilises some of the autophagic machinery to target external material eaten by cells, including pathogens and dead cells. This impacts many important processes within the cell. Using novel reagents and strategies developed in our lab, we are now exploring the role of this pathway in the immune system and extending our knowledge of its molecular regulation.

Progress in 2018

We have continued to build on previous successes with the publication of several papers from collaborators and our own lab. These results, and the development of a new mouse model by our lab, will extend our understanding of how cellular eating processes are regulated. Based on this success we obtained grant funding from BBSRC-UKRI to extend our work with a

Dynamics of autophagy in animal cells

Nicholas Ktistakis

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Senior postdoctoral researcher:
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Publications

www.babraham.ac.uk/our-research/signalling/nicholas-ktistakis

Michael Wakelam

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Lipids and their role in health and disease

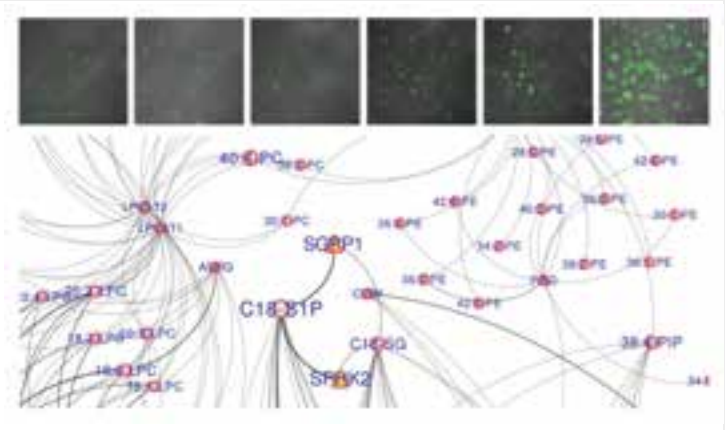
Lipids, also known as cellular fats, are highly dynamic structures with essential structural, metabolic and signalling roles. Our research aims to fully understand the physiological functions of lipids throughout the human lifespan. We use a multidisciplinary approach to identify the cellular signalling pathways and processes that individual lipid species regulate, and to investigate how the enzymes that determine the composition of the lipidome are regulated in response to changes in the environment.

Current Aims

Our present research is focused upon understanding the physiological importance of lipid molecular structures. By making use of cell and molecular biological methods coupled to lipidomics and bioinformatics we are determining the signalling and metabolic pathways that modify cellular lipids and how these are a ected by ageing, viral infection and diseases such as cancer. This work utilises cell lines and model systems in mice and C. elegans and allows us to identify potentially novel therapeutic targets to treat such conditions. We are also exploring the regulation of a number of enzymes involved in lipid signalling, fatty acid biosynthesis and metabolism, notably autotaxin, stearoyl CoA desaturase and acetyl CoA synthase.

Progress in 2018

During 2018 we have continued to build upon our lipidomics expertise through our role in maintaining and developing the LIPID MAPS platform. We completed and published the determination of novel therapeutic targets to treat rhinovirus infection of human bronchial epithelial cells by integrating our novel pathway analysis of lipidomics data. We made further use of this to de ne lipid enzyme changes in the liver and adipose of ageing mice and to identify which enzymes respond to dietary restriction and its reversal. Our ongoing studies into the importance of autotaxin and stearoyl CoA reductase demonstrated the importance of both in hepatitis C infection of liver cells.



Optimal subnetwork analysis comparing the lipidomes of uninfected and rhinovirus virus infected primary human bronchial epithelial cells. This method identi ed infection-related changes in the activities of a number of lipid metabolism and signalling pathways, providing a number of potential anti-rhinoviral targets.

Heidi Welch

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Anna Mandel (Left in 2018)
Anna Roberts (Left in 2018)

Cell signalling through Rac-GEFs

Rac is a protein that enables cells to attach and move through their

Publications

www.babraham.ac.uk/our-research/signalling/heidi-welch

Publications


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Welcome to the lipidome

Once neglected as too dull to study and too sticky to work with, lipids are at last stepping out of the shadows. Institute Director Michael Wakelam and lipidomics facility manager Andrea Lopez-Clavijo explain the challenges of working with these cellular Cinderellas and share their excitement of research in a field that's finally giving up its secrets.

For Professor Michael Wakelam, there's never been a better time to be studying lipids. On becoming the Institute's Director in 2007, he joined a thriving lipid research community. Things were very di erent, however, at the beginning of his career. "When I got my rst lectureship in 1985 I worried that all the good stu had been discovered," he remembers. "Now, I wonder how I can cram it all in before I retire. I wish I was just starting out again, because the things we can do are awesome."

Lipids are essential components of all our cells, but were for many years neglected by many scientists because they were di cult to study and seen as less exciting than genes or proteins. "They aren't easy to work with," Wakelam says. "They're not water soluble and some lipids stick to plastic. It can be painstaking work and until recently they were incredibly di cult to analyse and quantify."

Today, all that has changed. The Institute has played a central role in lipid research since the 1950s, but it's been the development of bioinformatics and mass-spectrometry over the past 20 years, together with the decision in 2016 that the Institute would co-host LIPID-MAPS, the world's largest lipid database, which has opened up the eld and fueled Wakelam's excitement.

We now know that as well as making up membranes and storing energy, lipids play a vital role in cellular signalling pathways. "They don't just hold things together and store energy. They're actually incredibly dynamic and regulate almost every function of the cell," he says. We have also discovered that the lipidome – which describes the total lipid landscape of our cells – is astonishingly complex and diverse. Thanks to new mass-spectrometry techniques, many of which were pioneered at the Institute, some 20,000 di erent lipid species from 30 distinct classes have so far been identi ed.

Structurally, lipids are proving fascinating too. Small di erences in lipid structure and saturation have major impacts on cell membranes: whether they are thick or thin, straight or curved, rigid or exible all depend on membranes' lipid makeup, with far-reaching implications for how immune cells work, how cancers spread and how viruses are able to infect our cells.

Lipidomics has exploded thanks to advances in mass-spectrometry. "It's allowed us to recognise an astonishing structural diversity in lipid molecules," says senior research fellow and expert analytical chemist Dr Andrea Lopez-Clavijo. "Without mass-spectrometry, we wouldn't have been able to determine what lipids were there and in what quantities. And without the bioinformatics capability to understand this data, all this would be pointless."

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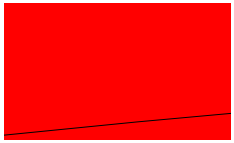

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