Chemical biology of mitochondria

Michael P. Murphy

MRC Mitochondrial Biology Unit, Hills Road, Cambridge CB2 0XY, UK

On 26–28 September 2016, the Theo Murphy (no relation) international scientific meeting on 'Chemical biology approaches to assessing and modulating mitochondria' was held at the Kavli Royal Society Centre, Chicheley Hall, Buckinghamshire, UK. Mike Murphy organized the meeting and it was enabled through the Royal Society scientific programme. The purpose of the conference was to bring together biologists, chemists and clinicians to discuss how to apply chemical biology to mitochondria to capitalize on the many new opportunities arising from the recent developments in mitochondrial biology.

Mitochondrial biology is now turning out to be important in many disparate areas of biomedical research. This may come as a surprise to those who remember mitochondria from their undergraduate days as being solely involved in metabolism and supplying ATP as a fuel. However, now many clinicians and biologists are finding that mitochondria are turning up unexpectedly in all sorts of areas of biomedical science, including ageing, neurodegeneration, cell death, obesity, diabetes, cancer and inflammation. Intriguingly, in these areas the role of mitochondria is often secondary to their metabolic roles and instead involves other biochemical processes such as the production of reactive oxygen species (ROS), changes in metabolite levels and the assembly of protein complexes as signalling hubs within and on mitochondria. These recent developments have emphasized the need to understand the multiple roles of mitochondria in biology. Furthermore, these findings also suggest that mitochondria are an important, but under-appreciated, drug target that can be used to develop new therapeutic approaches for many important diseases.

To achieve these goals, applying chemical biology to mitochondria has particular appeal, as it can help us both understand how mitochondria contribute to health and disease and also to develop new therapies. Therefore, this meeting on Chemical biology approaches to assessing and modulating mitochondria was organized with the goal of bringing together an interdisciplinary group of chemists, biologists and clinicians to develop new approaches and help nurture this rapidly developing field. In this theme issue of Interface Focus, the articles arising from this meeting are presented as a record of work to date and as a stimulus to future work.

The first article, which is from my laboratory and is by Logan & Murphy [1], provides an overview of the background to the application of chemical biology to mitochondria, and reviews what has been achieved to data as well as outlining the many possibilities and challenges ahead. From this general introduction, the following articles focus on particular aspects of the chemical biology of mitochondria. In the article by Hoogewijs et al. [2], 'Click Chemistry' is used to confirm whether or not a construct has made it successfully to the mitochondrial matrix, opening up the way to assessing the uptake of a range of constructs in the future.

One major way in which the development of mitochondria-targeted compounds has proved useful is in assessing the production of ROS by mitochondria and the laboratory of Liz New, which has provide many interesting new probes has reviewed this important field [3]. As well as targeting probes to mitochondria, it is also important to target potential drugs to mitochondria. Raman Kalyanaraman [4] has provided an overview of recent work on targeting the diabetes drug metformin to mitochondria in order to enhance its anti-cancer effects. This is particularly interesting as it shows how modifying
an existing drug to target it to mitochondria alters its efficacy and also builds on recent work suggesting mitochondria as a potential drug target in cancer. As well as using small molecules to assess mitochondria, a complementary approach is to use fluorescent proteins targeted to mitochondria that can be modified so as to respond to redox alteration in a range of cell compartments, including the mitochondrial matrix. The application of these approaches to mitochondria is covered by a leader in this field [5].

As well as targeting mitochondria, chemical biology can be applied to understand mitochondrial processes. The next article from Galkin & Moncada [6] focuses on applying chemical biology approaches to a particular aspect of mitochondrial function, the active/deactive transition in complex I, which provides an intriguing target that can be modified by targeted drugs [6]. Recently, it has become clear that the movement of metabolites such as succinate and fumarate from the mitochondrion to the cytosol and nucleus is major way in which changes in mitochondrial function contribute to the regulation of gene expression. Frezza [7], a pioneer in this emerging field, has provided an elegant overview of this area.

In addition to developing probes and drugs, an important aspect of applying chemical biology to mitochondria is to help understanding the interplay between mitochondria and cell mediated by small and evanescent signalling molecules such as NO and H₂S. To address this important area, Filipovic [8] has assessed recent technical aspects of understanding how NO and H₂S may work together to coordinate their signalling.

Together these articles provide a flavour of the many ways in which chemical biology can be applied to mitochondria, both to unravel their biological roles and to develop new therapies. Hopefully this collection of articles will spur others to apply interdisciplinary approaches to help us understand and modulate these fascinating organelles that are at the heart of so many areas of biology.

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References