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Centro Singular de Investigación en Química Biolóxica e Materiais Moleculares

Conferencia:

Manipulating mitochondrial ROS and oxidative damage as therapeutic strategies

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Manipulating mitochondrial ROS and oxidative damage as therapeutic strategies

Mitochondrial redox metabolism is central to the life and death of the cell. For example, mitochondrial production of free radicals and subsequent oxidative damage has long been known to contribute to damage in conditions such as ischaemia-reperfusion (IR) injury in stroke and heart attack. More recently mitochondrial redox changes have also been implicated in redox signalling. Over the past years we have developed a series of mitochondria-targeted compounds designed to ameliorate or determine how these changes occur. I will outline some of this work, which suggested that ROS production in IR injury during stroke was mainly coming from complex I. This led us to investigate the mechanism of the ROS production and using a metabolomic approach we found that the ROS production in IR injury came from the accumulation of succinate during ischaemia that then drove mitochondrial ROS production by reverse electron transport at complex I during reperfusion. This surprising mechanism led up to develop further new therapeutic approaches to impact on the damage that mitochondrial ROS do in pathology and also to explore how mitochondrial ROS can act as redox signals. I will discuss how these unexpected mechanisms may lead to redox and metabolic signals from mitochondria in a range of conditions under both healthy and pathological conditions.

Mike Murphy received his BA in chemistry at Trinity College, Dublin in 1984 and his PhD in Biochemistry at Cambridge University in 1987. After stints in the USA, Zimbabwe, and Ireland he took up a faculty position in the Biochemistry Department at the University of Otago, Dunedin, New Zealand in 1992. In 2001 he moved to the MRC Mitochondrial Biology Unit in Cambridge, UK (then called the MRC Dunn Human Nutrition Unit) where he is a group leader. Murphy's research focuses on the roles of reactive oxygen species in mitochondrial function and pathology. In particular he has pioneered the targeting of bioactive and probe molecules to mitochondria *in vivo*. This general methodology is now widely used. Prominent mitochondria-targeted compounds are antioxidants, such as MitoQ, which protects against oxidative damage in ischaemia-reperfusion injury. Murphy developed MitoQ as an oral drug which has been used in two Phase II trials so far. This work established mitochondria as a relevant drug target and opened up the field of mitochondrial pharmacology. The Murphy group has gone on to create MitoSNO, a mitochondria-targeted nitric oxide donor which is now being developed as a potential therapy for cardiac ischaemia-reperfusion injury, and MitoG to treat diabetes. Recently his work has extended to determining the mechanism by which mitochondria produce free radicals during ischaemia-reperfusion injury in heart attack and stroke. Murphy is a Wellcome Trust Investigator, honorary research Professor at the University of Otago, New Zealand, a recipient of the Keilin Medal from the Biochemical Society and is an honorary Fellow of the Royal Society of New Zealand. He has published more than 310 peer reviewed papers and has a h-index of 97.