Mitochondrial oxidative damage and human diseases

https://neurodegenerationresearch.eu/survey/mitochondrial-oxidative-damage-and-human-diseases/

Title of project or programme

Mitochondrial oxidative damage and human diseases

Principal Investigators of project/programme grant

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- United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

3964294.261

Start date of award

01-04-2005

Total duration of award in months

60

The project/programme is most relevant to

- Parkinson’s disease
- Neurodegenerative disease in general

Keywords

Mitochondria, oxidative damage, free radicals, antioxidants, mitochondrial DNA, human, mouse, yeast, neurodegeneration, apoptosis, necrosis.

Research abstract in English

Mitochondria are central to the function of human cells because they make energy available to the cell in a usable form and because they are central to a number of pathways of cell death. Consequently it is unsurprising that defects in mitochondrial function contribute to a number of human diseases, including neurodegenerative diseases such as Parkinson’s disease and Friedreich’s ataxia. Damage to mitochondria also contributes to the pathophysiology of heart attack, stroke and diabetes. In this project my group are developing new tools to target molecules to mitochondria in order to understand the processes by which mitochondrial damage occurs and to develop ways in which this damage can be prevented or repaired in human diseases.

In carrying out this work we seek to understand how mitochondrial damage occurs in yeast, cultured mammalian cells and in rodent models of mitochondrial damage. One of the most important causes of mitochondrial damage is thought to be the formation of free radicals by mitochondria as a byproduct of their normal function. These short lived but reactive species cause damage to mitochondria DNA, proteins and lipids thereby disrupting normal mitochondrial function. A consequence of this damage is that it causes cells to undergo cell death by both apoptotic and necrotic pathways. We are particularly interested in understanding the links between mitochondrial damage and increased cell death.

To unravel the role of mitochondrial free radicals in cell death requires a range of techniques from molecular biology, cell biology and biochemistry. In addition to these standard approaches, we are also developing a strategy that is proving to be particularly useful. This is the selective targeting of molecules to mitochondria within cells. To do this we use the large membrane potential across the mitochondrial inner member to drive the uptake of lipophilic cations to which we have attached biologically active molecules. These active molecules include antioxidants and reporter molecules designed to respond to free radicals. By using these molecules we are able to both estimate and block mitochondrial oxidative damage, and thereby infer its role in cell death. In related work we are also developing strategies to direct large molecules such as proteins and nucleic acids to mitochondria in order to repair the damage caused to mitochondria by free radicals.

The approaches we are developing may allow us to measure or manipulate mitochondria processes independently of the rest of the cell. This has scientific potential in helping us understand the roles of mitochondria within the cell. As some of the molecules being developed may prevent or repair mitochondrial damage they may lead to improved therapies for human diseases involving mitochondrial dysfunction. These include degenerative diseases such as Parkinson’s disease and diabetes and the general pathological changes associated with ageing.

Lay summary