Bacterial Complex 1

https://neurodegenerationresearch.eu/survey/bacterial-complex-1/

Title of project or programme

Bacterial Complex 1

Principal Investigators of project/programme grant

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- United Kingdom

Source of funding information

Medical Research Council

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3559963.45

Start date of award

01-04-2005

Total duration of award in months

60

The project/programme is most relevant to

- Neurodegenerative disease in general

Keywords

Respiratory chain; complex I; NADH:ubiquinone oxidoreductase; prokaryotic model;structural biology; single particle analysis; electron cryo-crystallography; X-ray crystallography; neurodegenerative diseases.

Research abstract in English

We will continue our efforts to determine a high resolution structure of bacterialNADH:ubiquinone

oxidoreductase (complex I). Research on this enzyme is increasing in importance as a growing number of human neurodegenerative diseases are being associated with mutations in complex I subunits. The structure of the complex will be needed to understand the effects of these mutations and to design drugs for treatment. The mechanism of the coupling between electron transfer and proton pumping also cannot be understood without a structure. Complex I is one of the largest known membrane proteins, and the simplest known version is the prokaryotic enzyme, which we are using as a ‘minimal’ model of the mammalian complex.

Lay Summary

Most of the energy required by humans is produced by the respiratory chain in mitochondria,which are ubiquitous cell organelles. This chain consists of five large membrane protein complexes, acting in concert to produce ATP, an energy-containing molecule used by our cells in metabolism. To understand how any protein works (or malfunctions in a disease) we need to know its atomic structure. Such structures are known for most components of the respiratory chain, except for the first and largest enzyme in the chain, complex I. This is not surprising, since complex I is one of the largest known membrane bound assemblies,consisting of 46 different subunits in mammals. Such large assemblies are difficult to crystallise for X-ray diffraction, the usual method for obtaining atomic structure. Knowledge of the structure of complex I will be indispensable for the design of drugs for treatment of a number of human neurodegenerative diseases (including Parkinson’s), which are associated with mutations in complex I subunits. We aim to obtain the structure of the much simpler bacterial complex I as a minimal model of the human enzyme and to study its mechanism.Our main experimental approaches to structural analysis are electron microscopy of two dimensional crystals and single molecules of intact complex I, and X-ray crystallography of its smaller subcomplexes. For mechanistic studies we shall use protein-film voltammetry and mutational analysis.