Structural analysis of the Parkinson’s associated kinase PINK1

https://neurodegenerationresearch.eu/survey/structural-analysis-of-the-parkinsons-associated-kinase-pink1/

Principal Investigators

Dr Miratul Muqit

Institution

University of Dundee

Contact information of lead PI
Country

United Kingdom

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1

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Research Abstract
Autosomal recessive inherited mutations in the PINK1 gene cause Parkinson’s disease (PD). PINK1 encodes a protein kinase that is unusual due to the presence of loop insertions within its kinase domain and a C-terminus of unknown function. Most human mutations are located within the kinase domain or perturb the C-terminus. To date analysis of human PINK1 has been hampered by poor expression and lack of significant catalytic activity in vitro. We have previously discovered catalytically active insect orthologues of PINK1 including Tribolium castaneum (TcPINK1). We wish to exploit TcPINK1 to determine the crystal structure of PINK1 and reveal the molecular basis of human mutations. Preliminary expression and analysis of a catalytic domain-containing fragment of TcPINK1 has enabled us to obtain crystals that diffract

to approximately ~6 Å. We aim to optimize crystallization conditions to generate new crystals that will enable solution of a high-resolution structure of TcPINK1. We will also investigate the molecular mechanism of how PINK1 targets its substrates and aim to solve a high resolution crystal structure of TcPINK1 bound to its substrates, ubiquitin and/or the Ubiquitin-like domain of Parkin. Finally we will employ mutagenesis approaches and biochemical studies to validate the TcPINK1 and co-complex structures. Overall these studies should provide new fundamental insights into how PINK1 mutations cause PD.

Further information available at:

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