Understanding the functions of LKB1 and other protein kinases mutated in inherited diseases

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Title of project or programme

Understanding the functions of LKB1 and other protein kinases mutated in inherited diseases

Principal Investigators of project/programme grant

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Address of institution of lead PI

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United Kingdom

Source of funding information

Medical Research Council

Total sum awarded (Euro)

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Start date of award

01-04-2005

Total duration of award in months

60

The project/programme is most relevant to

- Alzheimer’s disease and other dementias
- Parkinson’s disease

Keywords

Cancer, Hypertension, Parkinson’s disease, Diabetes, Protein Kinases, LKB1, AMPK, WNK1 and LRRK2

Research abstract in English

Protein kinases are the largest family of enzymes encoded by the human genome and their role is to catalyse the covalent attachment of phosphate to specific amino acid residues in target proteins. This modifies the functions of the target proteins and hence the physiological processes in which they participate. A highlight of our recent research has been the discovery of how the protein kinase LKB1 works. We found that, to be active, LKB1 must exist as a complex with two other proteins, termed STRAD and MO25. This allows LKB1 to activate AMPK, another protein kinase that is the major sensor of the energy status of living cells. Intriguingly metformin, the most widely prescribed drug to treat Type 2-diabetes, also exerts its effects by activating AMPK. By creating a strain of mice that do not express LKB1 in muscle, we were able to demonstrate that LKB1 and AMPK regulate the uptake of glucose into muscle during exercise. These finding were most unexpected, since the gene encoding LKB1 is mutated in Peutz-Jegers syndrome, an inherited disease that predisposes to multiple cancers, implying that LKB1 functions as a tumour suppressor in cells. We therefore wondered whether metformin, might not only have efficacy for the treatment of diabetes, but also for the treatment or prevention of cancer. Excitingly, a pilot epidemiology-based study involving a few thousand patients, which was undertaken in collaboration with Andrew Morris, Professor of Diabetic Medicine at Dundee, has indicated that diabetic patients in the Tayside region of Scotland have a significantly reduced risk of developing cancer if they are taking metformin. We have also demonstrated that LKB1 not only activates AMPK, but 12 other related protein kinases. These include protein kinases that control cell polarity and have been implicated in producing “neurofibrillary tangles”, which are the deposits found in the brains of patients with Alzheimer’s disease. Our future studies will focus on defining the cellular functions of the protein kinases that are activated by LKB1, which are poorly understood at present. We also plan to understand the roles of other poorly characterised protein kinases, whose mutation in humans results in inherited diseases. These include the WNK1 and WNK4 genes that are mutated in patients with Gordon s syndrome, an inherited hypertension syndrome, as well as the PINK1 and LRRK2 genes, which are mutated in people with early onset Parkinson’s disease. These studies have the potential to lead to the discovery of new regulatory pathways of relevance to the understanding of human disease.

Lay Summary