How does the PINK1 gene cause nerve cell death in Parkinson’s?

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<thead>
<tr>
<th>Project information</th>
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<tbody>
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<td>Lead researcher</td>
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<td>Start date</td>
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<td>Type of project</td>
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<td>Project code</td>
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**Project background**

In order to develop better treatments and ultimately a cure for Parkinson’s we need to understand what happens when a nerve cell starts to die. Then we may be able to identify ways to block this and slow down or halt the death of the specific nerve cells. A small number of people – probably less than 5% - have an inherited form of Parkinson’s. By examining the genes involved, we can get vital clues as to what is going on within a nerve cell when it starts to die. One of these genes is called *PINK1*.

- **Proteins which are newly made within a cell often need to be changed slightly before they can work properly.** This activation process can involve the addition of a chemical structure termed phosphate and this is done by an enzyme called a kinase. There are many types of kinase in a cell and these are very important to ensure that all of the machinery inside the cell works correctly. One of these enzymes is the PINK1 protein that is produced by the *PINK1* gene.

- **Changes in the PINK1 gene**, called mutations, are present in some people with an inherited form of Parkinson’s. So understanding what PINK1 does provides vital information about the causes of Parkinson’s and why specific of nerve cells are affected.
• **Mitochondria are like tiny power stations inside cells.** Nerve cells need lots of energy, for example to communicate with each other or to make important chemicals such as dopamine. So healthy mitochondria are vital for healthy nerve cells.

**What the researchers are doing**

Previous research showed that PINK1 is vital for the mitochondria in nerve cells to work correctly. If they contain the mutant form of the protein, the cell is no longer to make enough energy. This may explain why specific nerve cells in people with a mutation in PINK1 that is associated with inherited Parkinson’s are much more likely to die. Dr Abramov’s research aims to understand why the mutant form of PINK1 prevents the cells from making enough energy to survive. Armed with this knowledge, we may be able to devise new treatments to overcome the problem.

**Progress so far**

• The reason why mitochondria in nerve cells with the altered form of the PINK1 protein don’t work correctly is because they can’t control the amount of calcium that they contain. This is normally very well secured within the cell but leaks can prevent the mitochondria from producing enough energy and make them much more fragile.

• Dopamine is the chemical that is depleted in the brains of people with Parkinson’s due to the death of specific nerve cells. One of the roles of dopamine is to modify the amount of calcium entering the cell. Nerve cells can usually cope with changes in calcium due to changes in the level of dopamine because of the strict control processes. However, cells with mutant PINK1 are no longer capable of this and dopamine can now become toxic to the cells.

**What is the next stage?**

Because of the success of the initial three year project, Dr Abramov has been awarded a two year extension to his grant to see how he can expand on the results that he obtained.
and use them to develop potential new therapies for Parkinson’s. He will ask three questions:

- Why do only certain nerve cells die in Parkinson’s even though many will have problems manufacturing enough energy to survive?
- Are the problems with controlling the cell calcium levels due to the mutant PINK1 also seen in other forms of Parkinson’s, particularly those that may be caused by other genetic changes?
- Can treatment of nerve cells with chemicals to increase energy production by the mitochondria overcome the problems associated with Parkinson’s?

How the research will help people with Parkinson’s

If we can understand what happens within the brain when nerve cells die, this may help to provide new ways of developing drugs to slow down, halt or even reverse the process. In the first part of the study, Dr Abramov has obtained vital information about the key role of mitochondria in the death of nerve cells. He will now make use of this information to investigate whether there are chemical compounds that can overcome these problems and make the cells more robust.
Publications by the research team


For more information, please talk to the Research Team

Call 020 7963 9313
Email research@parkinsons.org.uk
Write Parkinson’s UK, 215 Vauxhall Bridge Road, London SW1V 1EJ