Otago family reveals genetic secrets

Researchers from the University of Otago have worked with a New Zealand family to unlock genetic secrets that may hold the key to fighting illnesses such as cancer and Alzheimer's disease.

The project, which received funding from the HRC, has identified a mutation that causes low blood platelet counts because of premature 'death' of platelet-producing cells in the bone marrow. By understanding the death pathways that affect platelet formation, their ongoing work may enhance treatments for diseases involving abnormal cell death.

Dr Ian Morison, from Otago's Department of Biochemistry, explained that his curiosity was triggered about ten years ago when a member of the science faculty was diagnosed with low blood platelets, resulting in surgery being cancelled.

"By testing her mother and then other family members, we soon knew we had found a hereditary condition that had never before been described," he said.

They were helped by a family tree that dated back to the 18th century – when the woman's ancestors were mining tin in Cornwall – and gathered blood samples from 80 family members. About 30 were found to have low platelets.

The team then began to search for the gene responsible. "It was one of those amazing needle in a haystack stories, looking among the three billion letters of DNA for a single misspelt letter that was shared by this family but not by others," Dr Morison said.

After three years, the researchers had narrowed it down to a small section of the genome with only one million letters. With the help of Pacific Edge Biotechnology Ltd, they discovered the single letter mutation. The mutation affected cytochrome c, a well-known protein that is an essential part of a cell's energy production.

Bringing Otago biochemist and protein expert Dr Liz Ledgerwood into the team, they then unravelled the reason for the low platelets. The mutation does not affect energy production, but the cytochrome c is better at triggering cell death, which is necessary for maintaining the correct number of cells in the body.

Dr Ledgerwood said what was surprising was that the mutation affected part of the protein that has "remained exactly the same for two billion years across a broad range of living organisms, from yeast to the grey whale".

Dr Morison said the project had evolved into an international collaboration involving other groups in the biochemistry department, protein experts in the US and Paris-based platelet expert Professor Elisabeth Cramer-Bordé, from the Institut Cochin, who found that platelet production was remarkably abnormal.

It was discovered that megakaryocytes, which are the bone marrow cells that produce platelets, were dying early and releasing their platelets into the bone marrow space, instead of into the circulation.

Dr Ledgerwood said "Correctly-controlled cell death is very important. In cancer, cells don't die when they should, while in Alzheimer's disease they die prematurely. Using the information gained from studying this unique New Zealand family, we hope to be able both to develop new ways to modify the death process and to understand when it is worthwhile to target cytochrome c-induced death. This may help treat some of the diseases that involve abnormal cell death in the future."

The research was supported by an HRC strategic development grant.

Dr Ian Morison and
Dr Liz Ledgerwood

Key words:
- Cancer, Alzheimer's disease, cytochrome c, low blood platelets

Key facts:
- Cytochrome c is a well-known protein that is an essential part of a cell's energy production

- In cancer, cells don't die when they should, while in Alzheimer's disease they die prematurely

Aims of this research:
- To understand cell death and help treat diseases that involve abnormal cell death

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