

How yeast is helping us to understand Parkinson's Disease

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Teams of scientists from Australia and the United States have used yeast and mammalian cells to discover a connection between genetic and environmental causes of Parkinson's disease.

Yeasts are single cell organisms, used widely in biological research because their structure resembles that of cells found in animals and humans. Yeasts share many genes, or their functional equivalents, with humans and offer the ability to screen or test thousands of genes and analysing their effects.

Two genes (alpha-synuclein and PARK9) had separately been associated with forms of Parkinson's disease, while manganese poisoning can cause PD-like symptoms in miners and welders exposed to high manganese levels. Findings connecting alpha-synuclein, PARK9 and sensitivity to manganese, made possible by yeast research, have been published online in the February issue of the prestigious international journal, *Nature Genetics*.

"This is the first time that we've been able to connect three pieces of the Parkinson's disease jigsaw puzzle and it tells us we're on the right track to understanding what goes wrong in this disease" said Dr Antony Cooper from Sydney's Garvan Institute of Medical Research and head of the project group in Australia.

Parkinson's disease involves the degeneration of neurons that produce the neurotransmitter dopamine. Autopsies show an abundance of the

small protein alpha-synuclein in affected regions of the brain, so scientists have known for some time that over-expression of the protein is toxic.

When a European group discovered PARK9's involvement in an inherited form of Parkinson's disease they examined some of the surviving neurons from patients who had 'sporadic' Parkinson's, as opposed to inherited forms of the disease, and found they contained ten times the levels of PARK9 when compared with similar parts of the brain in patients without the disease.

"Its possible that the surviving neurons remained functional, unlike the degenerated neurons surrounding them, because high levels of PARK9 protected them in some way," said Cooper.

"Little was known of PARK9's function but as yeast contains an equivalent gene, we were able to analyse its function."

"We found that high levels of the PARK9 in a cell diminish the toxic effects of alpha-synuclein. We also found that it appears to be a manganese pump, capable in theory of removing excess levels of the metal from cells."

"We need to know what is happening at the critical early stages of the disease, so that we can stop it, but we only get to examine human brains after death, when the damage has been done. Using yeast allows us to examine the early damaging stages."

A key, and perplexing, question for researchers in the field has been whether or not there is a single cause, or related group of genetic determinants, that result in dopaminergic neuron loss, or 'Parkinson's disease'.

"We would love to be able to link all the genes that we know have something to do with Parkinson's disease," said Cooper. "If you discover there's a central pathway involved, it provides much better potential for finding a successful treatment"

"So far, we've linked PARK9, alpha-synuclein and manganese toxicity. These linkages are not coincidental. They're likely to be affecting a pathway and we suspect it's a central pathway. To confirm that would be very exciting indeed."

Dr Cooper has been collaborating for several years with Dr Susan Lindquist, from the Whitehead Institute for Biomedical Research and Dr Aaron Gitler, from the University of Pennsylvania School of Medicine, to find how alpha-synuclein can damage cells.

To confirm that their results were not specific to yeast alone, Gitler, Cooper and Lindquist collaborated with Associate Professor Guy Caldwell, from the University of Alabama, and Associate Professor Jean-Christophe Rochet from the University of Purdue in Indiana, who verified their results in other Parkinson model systems.

"We wanted to check our findings were relevant in other Parkinson's models, because the more models it fits into, the more you believe it's real," said Cooper.

Source: Research Australia

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