Hereditary neurodegeneration linked to ADP-ribose modification

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Attaching chains of the small molecule ADP-ribose to proteins is important for a cell's survival and the repair of DNA damage, making this process a promising target for the development of new cancer drugs. Researchers have now identified a much sought after enzyme that removes such ADP-ribose modifications from proteins by studying a genetic mutation that causes neurodegenerative disease in humans. These findings, published today in *The EMBO Journal*, suggest that not only addition but also removal of ADP-ribose from proteins is essential for normal cell function.

Poly(ADP-ribose) chains have key roles in the repair of cellular DNA damage, as well as in the control of gene expression and cell death. Pharmacological drugs called PARP inhibitors prevent the addition of ADP-ribose or ADP-ribose polymers to proteins. Several of these drugs are undergoing clinical trials for the treatment of different types of cancers.

EMBO Young Investigator Ivan Ahel, a group leader at the Paterson Institute for Cancer Research at the University of Manchester, has been studying the underlying molecular processes, including an enzyme that shortens such chains piece by piece. "An enzyme that could completely uncouple ADP-ribose from proteins has remained elusive, even though such a cellular activity has been known to exist for more than 30 years," commented Ahel. "Our approach has been to combine clinical, biochemical and structural studies to see if we could pin point this enzyme activity in humans."

The eventual breakthrough came when Ahel and his collaborators Scott Williams (National Institutes of Health, USA), Gyula Timinszky and Andreas Ladurner (both from Ludwig Maximilians University Munich) teamed up with a group of clinical geneticists lead by Reza Sharifi at the Human Genetics Research Center at St George's University of London. "By studying genetic mutations in a group of patients with severe neurodegenerative disease, we found a gene that was mutated in a family that had several cases of severe progressive neurodegenerative and seizure disorder," remarked Sharifi. The product of this gene, which was named TARG1 (for terminal ADP-ribose protein glycohydrolase), exhibited the long-sought-after enzyme activity that fully removes ADP-ribose from proteins, and was further required for the proliferation of cells and response to DNA damage.

The researchers note that further work is needed to investigate the exact cellular processes where TARG exerts its functions, and to understand in more detail why mutation of this gene causes neurodegenerative disease. "Our discovery suggests a new pathogenic mechanism that may operate in a wider range of neurodegenerative disorders, the genetics of which generally remain very poorly understood," concluded Sharifi.

More information: Deficiency of terminal ADP-ribose protein glycohydrolase TARG1/C6orf130 in neurodegenerative disease, doi: 10.1038/emboj.2013.51

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