

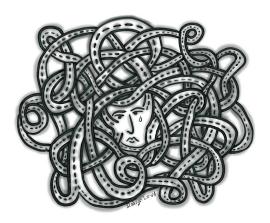
ONE MONTH, ONE PROTEIN <

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## life's tremors

Vivienne Baillie Gerritsen

Destruction is sometimes necessary for life to continue. It may sound paradoxical but examples are many. Our body shreds the food we eat to use the parts to feed itself. Certain cells commit suicide when they are of no use anymore. And damaged proteins within our cells are degraded and disposed of before they do any harm. Unsurprisingly, these are processes which involve multiple molecular interactions and are part of complex biochemical pathways – and when something goes wrong, our body is likely to feel the consequences. There is growing evidence that Parkinson's disease (PD) may well be caused by the accumulation, in certain neurons, of damaged proteins which – under normal circumstances – would have been degraded. Whether it is the accumulation of non-degraded proteins or the subsequent modified turnover of specific proteins which are the cause of PD, no one knows. But scientists have discovered one particular protein, suitably baptised "Parkin", which seems to be at the heart of the matter.



 $^{\mbox{\tiny CP}}$  Road Tears (2011), by Robyn Michele Levy\*

Courtesy of the artist

Parkinson's disease was named after the scientist cum politician James Parkinson (1755-1824) who was the first to describe what he called *Paralysis agitans*, or the Shaking Palsy. Apparently he never examined anyone in depth, but made keen observations on six individuals whilst on his daily strolls, sometimes inquiring into the history of their symptoms. Indeed, it is less for his activities as a surgeon, geologist, palaeontologist or political activist that Parkinson is known but more for the publication

of his now classical "Essay on the Shaking Palsy", written in 1817. And, as a tribute to his pioneering observations, the French neurologist Jean-Martin Charcot (1825-1893) renamed the illness "Parkinson's Disease" 60 years later.

There are two prevalent neurodegenerative disorders, one of which is PD - an infliction most of us are acquainted with. We have all encountered people whose hands tremble unceasingly - a common symptom of PD. Others, which are perhaps less obvious, involve rigidity, slowness of movement and balance problems. This is due to the death of specific neurons involved in dopamine transmission. Dopamine is part of many brain activities, including voluntary movement, sleep, mood, attention and motivation. People are usually inflicted with PD after the age of 50 but, in some cases, the first symptoms can occur at a far earlier age. Currently, scientists believe that some early forms of PD are the fruit of mutations in the protein Parkin - mutations which can be inherited.

As always, it was the discovery of mutations in Parkin that led to the understanding of its role within neurons in the first place. In particular, Parkin seems to be involved in the process which gets rid of damaged proteins within dopamine-containing neurons. Damaged proteins, hence undesirable proteins, must be cleared to sustain a proper turnover of any given protein. How does Parkin do this? In a nutshell, Parkin is able to add small molecules – known as ubiquitin – in a totem-like way, onto a protein that is defective. The resulting ubiquitin tag on the protein's surface acts as a signal for a proteasome, which will spy the tagged protein and subsequently degrade it.

The molecular structure of Parkin is quite well known. Its N-terminus is ubiquitin-like, while its C-terminus is reminiscent of the E3 ubiquitin-ligase family, i.e. a domain which involves one IBR (for In Between Region...) domain sandwiched between two RING (for Really Interesting New Gene...) fingers. The second RING finger binds the E2 ubiquitinconjugating enzyme. In turn, Parkin is able to act as an E3 ubiquitin-ligase and recognises its target protein via its N-terminal, to which it will add ubiquitin.

In particular, one of Parkin's target proteins in dopamine-containing neurons seems to be CD-Crel-1, a synaptic protein. A protein of relevance since it is involved in the proper function of the synaptic vessels which transmit dopamine from one neuron to another. If, for any given reason, Parkin is defective, it will cause an imbalance in CD-Crel-1 turnover, which is bound to have an effect on dopamine transmission, hence in brain activities such as involuntary movement for example.

It certainly seems to be the perfect explanation. However, this is just one theory. PD is a complex disease. Scientists are well aware that there are many mutations in Parkin which are capable of causing PD. What is more, these mutations may well have different effects on different proteins – each of which have a different role. And Parkin is not the only gene known to be involved in Parkinson's... As always, only part of the way has been paved. Yet it is an important one. The knowledge of the intimate structure of Parkin could ultimately lead to the development of therapies which would adjust protein turnover and keep dopamine-containing neurons alive.

\* Robyn Michele Levy is a visual artist, radio broadcaster, and writer. At age 43, she was diagnosed with Parkinson's disease and, eight months later, with breast cancer, and has just written her memoir: "Most of Me: Surviving My Medical Meltdown". She lives with her family and her remaining body parts in Vancouver, British Columbia.

## **Cross-references to UniProt**

E3 ubiquitin-protein ligase parkin, Homo sapiens (Human) : O60260

## References

- Beasley S.A. Hristova V.A., Shaw G.S. Structure of the Parkin in-between-ring domain provides insights for E3-ligase dysfunction in autosomal recessive Parkinson's disease PNAS: 104:3095-3100(2007) PMID: 17360614
- Zhang Y., Gao J., Chung K.K.K., Dawson V.L., Dawson T.M. Parkin functions as an E2-dependent ubiquitin-protein ligase and promotes the degradation of the synaptic vesicle-associated proein, CDCrel-1 PNAS 97:13354-13359(2000) PMID: 11078524
- Shimura H., Hattori N., Kubo S.-I., Mizuno Y., Asakawa S., Minoshima S., Shimizu N., Iwai K., Chiba T., Tanaka K., Suzuki T. Familial Parkinson disease gene product, parkin, is a ubiquitin-protein ligase Nature Genetics 25:302-305(2000) PMID: 10888878

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