

Lay Abstract

Parkinson's disease (PD) is an incurable neurodegenerative disease that affects all age groups but is most prevalent in elderly individuals, with more than 1% of the population older than 60 years of age suffer from it. According to United Nations estimates, there will be 2.1 billion people older than age 60 years in 2050, which translates into 21 million people older than 60 years suffering from PD. The main cause of PD is the accumulation and aggregation of a protein called alpha-Synuclein (alpha-Syn) in the brain cells of affected individuals. There is ample evidence showing that lowering alpha-Syn protein levels can benefit PD patients, and several clinical trials are currently focusing on lowering alpha-Syn levels using experimental medical reagents or vaccines.

One cellular RNA (miRNA-7/miR-7) has been shown to negatively regulate alpha-Syn production (encoded by the *SCNA* gene). miRs inhibit protein formation by binding to the messenger RNAs (mRNAs) that encode proteins. By binding to *SCNA* mRNA, miR-7 blocks alpha-Syn production, maintaining a normal level in healthy individuals. It has been shown that the levels of miR-7, as well as other miRs such as miR-153, which also negatively affect alpha-Syn production, are reduced in PD, allowing alpha-Syn overproduction and accumulation.

We and other researchers have shown that the HuR protein is a naturally occurring inhibitor of miR-7 production in human nonneuronal cells. In contrast, low levels of miR-7 indicate high alpha-Syn levels. HuR directly binds and stabilises *SCNA* mRNA and therefore further increases alpha-Syn levels in human cells. Interestingly, HuR activity and levels are enhanced in PD and other incurable human diseases, such as cancer. Additionally, HuR is known to upregulate TNF-alpha protein upregulated in PD, responsible for contributing to inflammation and neuronal degeneration. Thus, I hypothesise that targeting HuR-RNA interactions may contribute to the lowering alpha-Syn and TNF-alpha levels in human neuronal cells and could be used for future PD therapy. I also hypothesise that the nematode *C. elegans* is an excellent model organism to study this axis as it carries the only close homologue of HuR, *exc-7*, and presents a PD phenotype when it is forced to produce human alpha-Syn.

Finally, our preliminary data show that the production of miR-153, which negatively regulates alpha-Syn protein expression, is blocked in cultured human neuronal cells. I therefore hypothesise that miR-153 is regulated by a naturally occurring inhibitor and that increasing the production or blocking the interaction of this inhibitor with miR-153 will lead to a synergistic and/or additive effect to inhibit alpha-Syn production and alleviate PD symptoms.

The project aims to test these hypotheses using advanced molecular methods, cell biology, a model organism, and a multidisciplinary international team of experts. Understanding and intervening in the RNA regulatory networks involved in the aetiology of PD may provide new avenues to therapy for PD and other diseases associated with disorders of gene expression and RNA metabolism.