Targeting the mRNA of 'undruggable' proteins in the fight against Parkinson's disease

January 8 2024, by Justin Jackson

Credit: Pixabay/CC0 Public Domain

Researchers at the Scripps Research Institute, Florida, have developed a new method to counteract α-synuclein protein levels by targeting the

mRNA that forms them. The strategy unlocks many research doors with potential therapeutic approaches for addressing neurodegenerative diseases.

In a paper, "Decreasing the intrinsically disordered protein α-synuclein levels by targeting its structured mRNA with a ribonuclease-targeting chimera," published in *PNAS*, the team introduces Synucleozid-2.0 and Syn-RiboTAC, an mRNA binding and degradation duo that allowed modulation of the highly undruggable protein, α-synuclein, by targeting its encoding mRNA.

Neurodegenerative diseases, especially Parkinson's disease (PD), pose significant therapeutic challenges due to the difficulty in targeting specific proteins like α-synuclein, which have increased levels associated with disease progression.

Conventional methods, such as antibodies or antisense oligonucleotides, are limited when targeting intrinsically disordered proteins like α-synuclein as they lack stable three-dimensional structures, typical small-molecule binding sites or pockets, which are often the conventional targets for drug compounds.

By creating a method to target the encoding mRNA structure before it forms the protein, the researchers created a tool that can bypass the difficulty of targeting the fully formed protein by limiting its initial production levels.

In PD patient-derived neurons, Syn-RiboTAC indirectly restored the expression of around half of the dysregulated genes. The reduction in α-synuclein levels likely allowed for the restoration of some dysregulated genes disrupted by its abnormal accumulation. The downstream effects of α-synuclein reduction could also alleviate cellular stresses, allowing cells to regain normal function and gene expression patterns.

The results are a breakthrough, illustrating that traditionally "undruggable" proteins like α-synuclein can be targeted via mRNA binding, expanding the druggability of disease-related proteins through small molecule binders and degraders.

As PD currently has no cure, effective symptom relief treatments are needed to maintain quality of life. The new strategy requires further research in a clinical therapeutic setting where many unmet medical needs urgently await expanded druggability of currently undruggable proteins.

More information: Yuquan Tong et al, Decreasing the intrinsically disordered protein α-synuclein levels by targeting its structured mRNA with a ribonuclease-targeting chimera, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2306682120