Molecular key may unlock new treatments for neurodegenerative disorders

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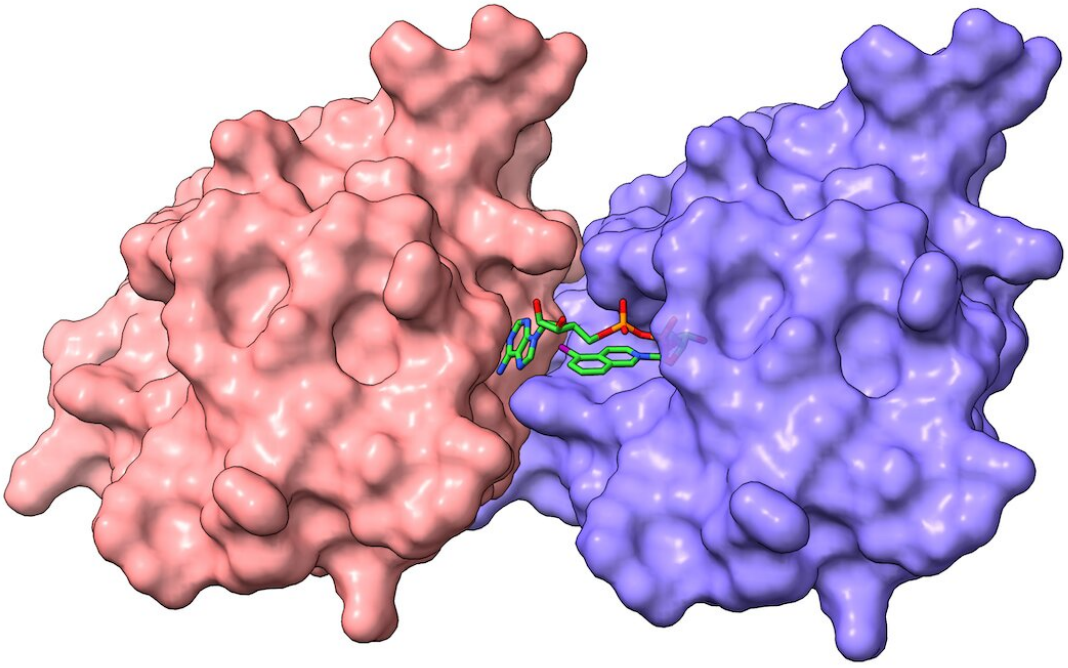

Structure of SARM1 in complex with inhibitor. Credit: Thomas Ve

Researchers have worked out how to successfully switch off a key pathway of nerve fiber breakdown in debilitating neurodegenerative disorders such as Parkinson's disease, traumatic brain injury and glaucoma.

The study, led by Griffith University's Institute for Glycomics and Disarm Therapeutics, a wholly owned subsidiary of pharmaceutical company Eli Lilly, reveals the structural processes behind activation and inhibition of SARM1, a key molecule in the destruction of nerve fibers.

"As a trigger for nerve fiber degeneration, understanding how the enzyme SARM1 works may help us treat several neurodegenerative conditions," said Dr. Thomas Ve from the Institute for Glycomics.

"In this study we show the molecular interactions that can switch SARM1 on and off. This gives us a clear avenue for the design of new drug therapeutics."

In neurodegenerative conditions like peripheral neuropathy, Parkinson's disease, amyotrophic lateral sclerosis (ALS), traumatic brain injury and glaucoma, when the nerve fibers are damaged, SARM1 is activated.

"This sparks a cascade of molecular processes that leads to the self-destruction of the nerve cell's axon, the cable that carries electric impulse away from the body of the nerve cell to the next,"' Dr. Ve said.

"Several times thinner than a human hair, but up to a meter in length for those that extend from the brain down the spinal cord, their destruction can lead to catastrophic dysfunction."

Co-author Dr. Yun Shi said the SARM1 protein acts like a sensor that responds to the environment.

"It switches on when the levels of a small activator molecule nicotinamide mononucleotide (NMN) increase. The activator binds to the larger SARM1 protein like a key in a lock, opening the door to the process that leads to the breakdown of the nerve fibers."

Once unlocked, SARM1 is able to break down another key molecule called nicotinamide adenine dinucleotide (NAD^+), a cellular fuel that nerve fibers need to function and stay alive.

The researchers used NMR spectroscopy to demonstrate how SARM1 consumes NAD^+ and, more importantly, reveal the molecular details involved in blocking this process.

"We introduced a chemical developed by our industry partner Disarm Therapeutics and demonstrated that it reacts with the NAD^+ molecule and binds tightly to SARM1 to prevent further breakdown of NAD^+.

The study also used structural biology tools (cryo-electron microscopy and X-ray crystallography) to determine for the first time a structure of SARM1 in complex with an inhibitor and to reveal the structural changes involved in opening the lock that activates SARM1.

"Moving forward, the goal is to build on these results, to make improved molecules to turn off this pathway which are more specific towards SARM1. If this can be achieved, it can ultimately lead to new treatments for patients suffering a variety of neurological conditions."

Professor Mark von Itzstein AO, Director of the Institute for Glycomics, welcomed this important breakthrough, discovered through the Institute's engagement with industry.

"New strategies towards solving neurodegenerative diseases have become increasingly important due to the enormous impact on the quality of life of those that suffer with these conditions."

The study has been published in the journal *Molecular Cell*. The Griffith team worked in collaboration with the group of Professor Bostjan Kobe at University of Queensland, and the groups of Professors Aaron DiAntonio and Jeffrey Milbrandt at Washington University, St Louis, U.S..

More information: Yun Shi et al, Structural basis of SARM1 activation, substrate recognition, and inhibition by small molecules, *Molecular Cell* (2022). DOI: 10.1016/j.molcel.2022.03.007

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