Unravelling the mysteries around type 2 diabetes

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For more than 30 years, scientists have been trying to unravel the mystery of how a key biological molecule self assembles into a rogue protein-like substance known as amyloid, which is thought to play a role

in the development of type 2 diabetes—a disease that affects 300 million people worldwide.

A team of scientists at the University of Leeds has, for the first time, been able to identify the step-by-step changes that take place in the molecule known as human islet amyloid polypeptide, or hIAPP, as it changes into amyloid.

They have also discovered new compounds that are able to speed up or slow down the process.

In healthy people, hIAPP is secreted by islets in the pancreas alongside the hormone insulin and it helps to regulate blood glucose levels and the amount of food in the stomach. When hIAPP malfunctions, it forms clumps of a protein-like substance called amyloid fibrils that kill the insulin-producing islets in the pancreas.

The build-up of amyloid fibrils is seen in people with type 2 diabetes although the exact mechanism of how it triggers disease is not known.

The research findings—Tuning the rate of aggregation of hIAPP into amyloid using small-molecule modulators of assembly—are published today in the journal *Nature Communications*.

The paper not only describes the complex molecular changes seen in hIAPP molecules as they transform into amyloid fibrils, but the scientists also announce that they have discovered two compounds, described as molecule modulators, which can control the process: one of the compounds delays it, the other accelerates it.

These molecule modulators can be used as "chemical tools" to help scientists investigate the way amyloid fibrils grow and how and why they become toxic.

Significantly they offer "starting points" for the development of drugs that could halt or control amyloid fibril formation and help in the urgent search to find ways to treat type 2 diabetes.

Sheena Radford, Royal Society Research Professor and Professor of Biophysics at the Astbury Centre for Structural Molecular Biology at Leeds, who supervised the research, said: "This is an exciting and huge step forward in our quest to understand and treat amyloid disease and to tackle a major health issue that is growing at an alarming rate.

"The compounds we have discovered are a first and important step towards small molecule intervention in a disease that has foxed scientists for generations."

The research team looked at hIAPP found commonly in the population and a rare variant found in people with a genetic mutation known as S20G which puts them at greater risk of developing type 2 diabetes.

Amyloid fibril formation linked to disease

Understanding amyloid fibril formation is a key area of health research. The formation of fibrils is believed to be a factor in a range of life-limiting illnesses including Alzheimer's Disease and Parkinson's Disease, as well as type 2 diabetes.

Professor Radford added: "The results are also hugely exciting as they open the door to using the same type of approaches to understanding other amyloid diseases, the vast majority of which currently lack any treatments."

More information: Tuning the rate of aggregation of hIAPP into amyloid using small-molecule modulators of assembly, *Nature Communications* (2022). DOI: 10.1038/s41467-022-28660-7

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