Secrets of longevity protein Klotho revealed, may help in finding therapies for multiple diseases

The 3D structure of the Klotho protein holds out promise for new therapies to treat a wide range of medical conditions, including diabetes, obesity and certain cancers.

Scientists have unveiled the 3D structure of a protein linked to longer lives, paving the way for new therapies to treat a wide range of medical conditions, including diabetes, obesity and certain cancers.

Named after the Greek goddess who spun the thread of life, Klotho proteins play an important role in the regulation of longevity and metabolism.

Researchers from Yale University in the United States revealed the three-dimensional structure of one of these proteins, beta- Klotho, illuminating its intricate mechanism and therapeutic potential.

The Klotho family of two receptor proteins are located on the surface of cells of specific tissues.

The proteins bind to a family of hormones, designated endocrine FGFs, that regulate critical metabolic processes in the liver, kidneys, and brain, among other organs.

To understand how beta-Klotho works, the research team used X-ray crystallography, a technique that provides high- resolution, 3D views of these proteins.

The researchers' analysis yielded several insights.

First, beta-Klotho is the primary receptor that binds to FGF21, a key hormone produced upon starvation.

When bound to beta-Klotho, FGF21 stimulates insulin sensitivity and glucose metabolism, causing weight loss.

This new understanding of beta-Klotho and FGF21 can guide the development of therapies for conditions such as type 2 diabetes in obese patients, the researchers said.

"Like insulin, FGF21 stimulates metabolism including glucose uptake," said Joseph Schlessinger from the Yale School of Medicine.

"In animals and in some clinical trials of FGF21, it shows that you can increase burning of calories without changing food intake, and we now understand how to improve the biological activity of FGF21," Mr. Schlessinger said.

The study, published in the journal *Nature*, also describes a new variant of FGF21 that has 10 times higher potency and cellular activity.

The team presented evidence of how a structurally-related enzyme, glycosidase, which breaks down sugars, evolved into a receptor for a hormone that lowers blood sugar — which may not be a coincidence, Mr. Schlessinger added.

Having untangled the structure of beta-Klotho, researchers have a platform for exploring potential therapies for multiple diseases.

By developing drugs that enhance the pathway, Mr. Schlessinger said, researchers can target

diabetes and obesity.

Conversely, using agents that block the pathway, they hope to explore therapies for conditions such as liver cancer and bone diseases, among others.

“The next step will be to make better hormones, make new potent blockers, do animal studies, and move forward,” Mr. Schlessinger said.

Astronauts on extended space travel missions would have significant bone and muscle complications.

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