Protein courtship revealed through chemist's lens

September 15 2014

Staying clear of diseases requires that the proteins in our cells cooperate with one another. But, it has been a well-guarded secret how tens of thousands of different proteins find the correct dancing partners as they degrade and build up the human body, brain and nervous system. A recent breakthrough at the University of Copenhagen's Department of Chemistry has busted down the door and provided a look at the once obscure behaviour on the protein dance floor.

Professor emeritus Jens Jørgen Led of the University of Copenhagen's Department of Chemistry and his colleagues have just published a method that helps reveal the secret dance of proteins in their article, "Specific and nonspecific interactions in ultra-weak protein-protein

associations revealed by solvent paramagnetic relaxation enhancement", in the latest edition of the pre-eminent *Journal of the American Chemical Society*.

Until now, it has been impossible to record how proteins actually find one another in living organisms. This posed a problem because a great many biological processes begin when two proteins meet and initiate a reaction. And when things go wrong, they can go extremely wrong. From diabetes to cystic fibrosis and Parkinson's, to severe forms of dementia such as Alzheimer's – many illnesses are linked to mis-folding of the proteins, or the proteins clustering together - a process known as protein aggregation.

Jens Jørgen Led is understandably proud of his discovery. "Anyone involved in pharmaceutical development or understanding disease can apply this method. In fact, I think this is the best research that I have ever taken part in," says Jens Jørgen Led.

When a protein such as a growth hormone must find its interaction partner (its so-called receptor) there are tens of thousands of protein partners to choose from. Therefore, proteins must be equipped with a mechanism allowing them to rapidly scan an enormous number of potential interaction partners. This mechanism, termed 'ultra-weak interaction', is where proteins influence one another through electrostatic forces. It can be compared to a dancer moving along a wall, asking girls for a dance. He begins with a bow, and only if the girl nods, he takes her hand and they venture onto the dance floor.

Ultra-weak interactions are so weak that it has so far been impossible to calculate them using mathematical tools, let alone investigate them by physical measurements. But Led and his group have developed a method that makes it possible to observe the ultra-weak interactions using NMR spectroscopy. A spectrometer makes it possible to investigate molecular

architecture by exposing molecules to a magnetic field. Led exploited the fact that one can observe a protein molecule's reaction in a magnetic field by deploying a paramagnetic substance called Gadodiamide. The substance is ideal for the task because it doesn't initiate chemical reactions with proteins, and therefore has no influence over protein structure. Furthermore, removing it is easy after measurement.

But changes in the protein NMR spectra are small and weak, so finding out whether the trick worked wasn't straightforward. "At first, we didn't know what we were looking at. It appeared to us as uncertainty in the data, and it was extremely time-consuming to unravel the system. I wouldn't have had the time to do this if I wasn't retired," says Jens Jørgen Led.

The new method makes it possible to see exactly how proteins bow and curtsey to one another during their dance floor courtship. This knowledge can be used in the production of proteins in an industrial setting, in the research of disease pathways and when developing new protein-based pharmaceuticals.

"It was already acknowledged that proteins found one another via ultra-weak interactions, but no one knew how to measure them. Now we can," states Led.

Jens Jørgen Led hopes that other researchers will take his discovery, incorporate it into their own work and develop the know-how so it can be used in living systems as well.

Provided by University of Copenhagen