Bacteria disarmer activates fiber formation in Parkinson's protein

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(PhysOrg.com) -- The same substance that hampers the infection capability of bacteria can hasten the fiber formation of the protein that is involved in the development of Parkinson's disease. The study shows how important basic research is to our understanding of possible side effects from drug candidates interacting with various target proteins.

The study was done by researchers at Umeå University in Sweden and is published in the latest issue of the prestigious *Journal of the American Chemical Society.* The findings surprise all the researchers involved.

Fredrik Almqvist, professor of organic chemistry, working with colleagues at Washington University in St. Louis and the University of Michigan in Ann Arbor, has developed a molecule, FN075, that slows down the infection capability of bacteria. This molecule blocks the growth and function of the hair-like shoots that bacteria use to cause infections. Even though the molecule is not used in any drugs today, this disarming principle could be of great importance in future struggles against resistance to antibiotics.

Interestingly, bacteria's hair-like shoots are structured according to the same principle as amyloid proteins, improperly folded proteins that accumulate in nerve disorders like Parkinson's and Alzheimer's diseases.

"So we tested whether FN 075 could also hamper the formation of amyloids in a protein that is implicated in Parkinson's disease. But instead it turned out that the molecule boosted the formation of amyloid

structures," says Pernilla Wittung-Stafshede, professor of biological chemistry.

In other words, the same tiny molecule can have exactly the opposite effect depending on what protein it encounters and in what surroundings. The study thus shows that it is important to test for possible side effects that new substances might have on amyloid proteins.

"There seems to be a fine balance between what activities these types of substances hamper and what activities they prompt," says Pernilla Wittung-Stafshede.

She says it is too early to say whether the effects on the amyloid proteins are positive or negative from a medical perspective. On the other hand, it is clear that molecules like FN075 are key research tools to achieve an understanding of these types of complex processes.

The new findings have inspired the researchers regarding how to continue to design and use small molecules that can affect amyloid formation.

"Perhaps some of the body's own small metabolites help to trigger amyloid formation in nerve disorders like Parkinson's and Alzheimer's,"wonders Fredrik Almqvist, who declares that they will now be following up these findings.

The research is being conducted at the Chemical Biology Centre, KBC, and the Umeå Centre for Microbial Research, UCMR at Umeå University and is based on the combined expertise of the chemists Pernilla Wittung-Stafshede, Magnus Wolf-Watz, and Fredrik Almqvist. Most of the study was carried out by post-doctoral fellows Istvan Horvath, Christoph F. Weise, and Emma Andersson. With the assistance of the KBC platform for nuclear magnetic resonance, NMR, the

scientists have been able to study proteins at the atomic level.

More information: Istvan Horvath, Christoph Felix Weise, Emma K. Andersson, Erik Chorell, Magnus Sellstedt, Christoffer Bengtsson, Anders Olofsson, Scott J. Hultgren, Matthew R Chapman, Magnus Wolf-Watz, Fredrik Almqvist, and Pernilla EL Wittung-Stafshede. Mechanisms of protein oligomerization: Inhibitor of functional amyloids templates α-synuclein fibrillation. *Journal of the American Chemical Society* 2012. DOI: 10.1021/ja209829m

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