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Behavior of Alzheimer's-linked protein is revealed

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Enzymes called kinases manage a wide range of cell processes, from metabolism, cell signaling, nutrient transport, and many others. Because they can affect so many different cell activities, kinases are tightly regulated within cells to make sure that the enzymes only act when necessary. Improperly activated kinases are linked to illnesses such as cancer and Alzheimer's disease. A group of scientists from VIB, Vrije Universiteit Brussel (VUB) and Université Libre de Bruxelles (ULB) led by Prof. Tom Lenaerts (VUB-ULB) and prof. Nico van Nuland (VIB-VUB) has uncovered a new mechanism for controlling the activation of a kinase implicated in Alzheimer's disease, generating novel insights into how to control this protein's activity.

The research was published in the high-profile journal *Structure*, a Cell Press periodical.

To make sure that the activities of kinase proteins are well-managed, proteins have evolved different methods to toggle them on and off by disrupting their interactions on a molecular level. Side chains are chemical groups directly attached to a protein's main chain or backbone that affect both the shape and function of a protein. In their new research on the activation of a specific enzyme called Fyn, Prof. Lenaerts and his team were able to identify the specific toggling mechanism that this protein uses to ensure its own regulation, revealing for the first time the role that side chains play in the process. Their observations may be important to the development of Alzheimer-treatment therapies, as Fyn interacts with the protein Tau, which has

been identified as a cause of the disease.

How cells switch their enzymes on and off

Just like the thermostats in our homes, which turn the heat on and off based on temperature changes, changes in the interactions between the modules defining protein structures activate and deactivate kinases. Using both experimental and predictive techniques, the multidisciplinary team uncovered a network of communicating protein residues inside cells that control Fyn's activation. Research has shown that toggling off Fyn in mice with Alzheimer's disease reduces memory problems in these mice.

Prof. Tom Lenaerts (VUB-ULB): "The insights presented by our research may provide important mechanistic knowledge of kinase regulatory systems, which could be used to develop new drugs that regulate Fyn's activity in Alzheimer's patients."

The human side of excellent science

This research is especially poignant to the Belgian scientific community, as Prof. Nico van Nuland, co-author and a pioneer in this research field, was diagnosed only a few years ago with Amyotrophic Lateral Sclerosis (ALS). He has been fighting this disease with courage and optimism, providing crucial support to the entire research team. He possesses expert knowledge of nuclear magnetic resonance spectroscopy, which was crucial in the reported research. "Without his contributions, these results would have never been realized," says Prof. Lenaerts.

More information: Radu Huculeci et al. Dynamically Coupled Residues within the SH2 Domain of FYN Are Key to Unlocking Its Activity, *Structure* (2016). DOI: 10.1016/j.str.2016.08.016

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