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Identification of the action mechanism of a protein impacting neural circuit development

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Research by Dr. Shernaz Bamji, from the University of British Columbia, uncovers the mechanism of action of an enzyme called DHHC9 in the normal development and function of neural networks in the brain. Mutations in DHHC9 have been identified in certain patients suffering from X-linked Intellectual Disability, however the specific role of DHHC9 was not known. Dr. Bamji's work shows this enzyme plays a vital role in promoting the growth and branching of the ends of neurons and also in maintaining the balance between excitatory and inhibitory signals being formed onto neurons (called excitatory and inhibitory synapses, respectively).

"To understand how genetic variants of DHHC9 identified in patients with X-linked Intellectual Disability, impact the development of neural circuits, we expressed them in neurons", says Shernaz Bamji. " We observed a severe reduction in the growth and branching of the neurons expressing these DHHC9 mutations. Moreover, there was a decrease in the number of inhibitory synapses being formed onto the neurons making the neurons more excitable. This is of great interest as a significant number of patients with X-linked Intellectual Disability are prone to seizures".

For proper brain development to occur, neurons must extend processes, branch, and make connections with other neurons. The Bamji laboratory has shown that a specific type of modification of neuronal proteins can impact all of the above processes and impact the proper development of the brain. This modification is called 'palmitoylation', and involves the

addition of a small fatty acid called palmitate onto a protein. The palmitoylation of proteins can have profound effects on their location within the neuron, which in turn can significantly impact the proper development and function of the neuron. Protein palmitoylation is mediated by a family of 23 DHHC proteins. Genetic variations in 9 of the 23 DHHC proteins have been identified in patients with diseases of the nervous system including a number of neurodegenerative and neurodevelopmental disorders. This underscores the importance of this family of proteins in the development and functioning of the brain.

Recent research in the Bamji laboratory has investigated the localisation and function of one such protein, called DHHC9. Her work has shown that DHHC9 is present in both neurons that activate and those that inhibit other neurons, and that it affects an important signaling molecule, called Ras GTPase. Adding a palmitate to Ras enhances its trafficking to the cell membrane, where it plays an important role in regulating the growth and the branching out of neurons, and the density of synapses, or connections, it forms with other cells.

Previous work in the Bamji laboratory had shown the importance of cell adhesion proteins, such as cadherins, in regulating synaptic plasticity. They had shown that a family of proteins inside the cell called catenins regulate the activity of cadherins, and that catenins themselves are regulated by palmitoylation. Another palmitate transferring protein, called DHHC5, mediated the addition of palmitate to catenins.

"We believe that a better understanding of the function of DHHC proteins will lead to a better understanding of the normal functioning of the brain, and will help identify novel targets for therapies aimed at correcting disorders that affect synapse form or function, including many neurodegenerative and psychiatric diseases", concludes Shernaz Bamji.