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Making the right connections

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Summary: Researchers have uncovered a new molecular interaction that governs the formation of specific functional connections between two types of neurons. It gives an important clue as to how unique interactions give shape to precisely organized neuronal networks in the brain.

FULL STORY

Researchers at VIB and KU Leuven have uncovered a new molecular interaction that governs the formation of specific functional connections between two types of neurons. It gives an important clue as to how unique interactions give shape to precisely organized neuronal networks in the brain.

Pyramidal neurons are named after their cell body, which is shaped like a pyramid with multiple long protrusions. Like large trees, these protrusions extend through multiple brain tissue layers where they make connections with both neighboring and more distant neurons.

A tree with many branches

"Pyramidal neurons are very complex cells," explains prof. Joris de Wit, who heads the lab of Synapse Biology at VIB and KU Leuven. "They receive signals through many different neuronal connections, or synapses, and this allows them to process various types of information."

This precise organization of connectivity is essential for normal brain function, but the mechanisms that orchestrate it are not well understood. "Our research is all about figuring out how this synaptic architecture is regulated in the brain," says de Wit.

In a new study published in *Neuron*, his team identifies a new protein interaction that mediates the formation of one very specific type of synapse, namely that between so-called mossy fibers and pyramidal neurons located in a specific region in the hippocampus, the brain area central to learning and memory.

A newly uncovered interaction

It all started with a hint in earlier findings of the research group. "We knew that proteins called glypicans are very important for synaptic development," says Giuseppe Condomitti, member of de Wit's team and first author on the study. "In our experiments we had observed that glypican 4 was present in large numbers on the mossy fibers, but we also knew that its previously identified binding partner wasn't present on pyramidal neurons. So there had to be something else going on here at this synapse."

Their curiosity led the scientists to identify a new interaction between glypican 4, a protein that has been linked to autism spectrum disorders and intellectual disability, and GPR158, a receptor that is located exclusively on the part of the pyramidal neuron's tree that receives connections from the mossy fibers.

"The specificity of the GPR158 receptor for this particular synapse was very surprising to us. Even if we overexpressed the receptor in pyramidal neurons, we still found it only at mossy fiber synapses," says de Wit. When the researchers removed GPR158, the structure and function of mossy fiber synapses was dramatically impaired. "But other connections on the pyramidal neurons were completely normal," adds Condomitti, "again showing that GPR158 specifically controls mossy fiber synapses."

In a collaboration with researchers at the Scripps Research Institute in the US, published on the same day in Cell Reports, de Wit and Condomitti helped demonstrate that a similar mechanism also controls connectivity in the retina, suggesting that the interaction they uncovered shapes connectivity in different parts of the brain.

Tip of the iceberg

Technological advances have enabled neuroscientists to study the brain at an increasingly detailed level, and the single-cell revolution is at full speed. These new research findings take it one step further, unravelling unique biological features at the resolution of specific connections.

"It is fascinating to see how unique molecular interactions give shape to different connections in the brain," continues de Wit. "I think that what we have seen so far is just the tip of the iceberg in terms of molecular diversity of brain connections. We have no idea yet what mechanisms may shape the other connections on pyramidal neurons. Understanding the molecular blue print of all connections in a brain region like the hippocampus will be a major challenge for years to come."

Story Source:

Materials provided by **VIB (the Flanders Institute for Biotechnology)**. *Note: Content may be edited for style and length.*

Journal References:

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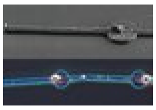

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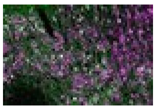

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