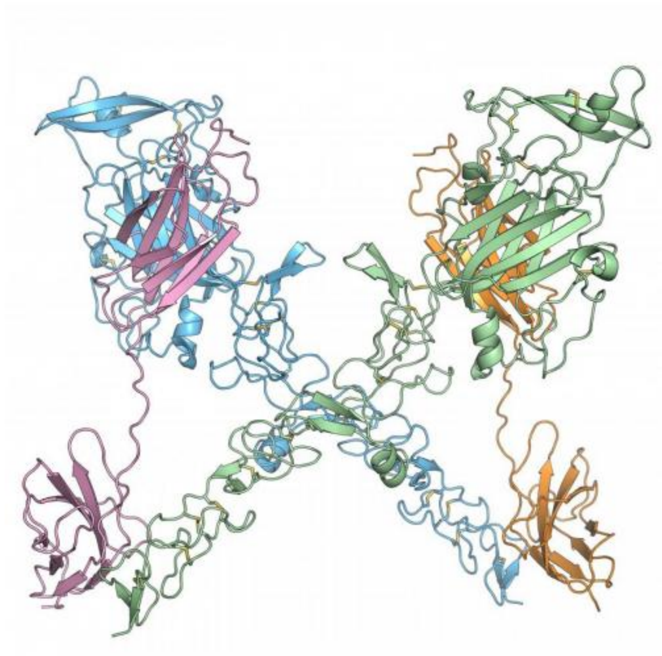
Research details how developing neurons sense a chemical cue

30 May 2014



Chemical cues help developing neurons make the right connections by telling them where to extend their branches, or axons. New structural studies of the interactions between one such cue and receptor molecules on the axons reveal how Netrin-1 molecules (blue and green) bind to two neogenin molecules (magenta and orange). Credit: Dimitar B. Nikolov

Symmetry is an inherent part of development. As an embryo, an organism's brain and spinal cord, like the rest of its body, organize themselves into left and right halves as they grow. But a certain set of nerve cells do something unusual: they cross from one side to the other. New research in mice delves into the details of the molecular interactions that help guide these neurons toward this anatomical boundary.

In an embryo, a neuron's branches, or axons, have special structures on their tips that sense chemical cues telling them where to grow. The new findings, by researchers at Memorial Sloan Kettering Cancer Center and The Rockefeller University, reveal the structural details of how one such cue, Netrin-1, interacts with two sensing molecules on the axons, DCC and a previously less well characterized player known as neogenin, as a part of this process.

"Our work provides the first high-resolution view of the molecular complexes that form on the surface of a developing axon and tell it to move in one direction or another," says Dimitar Nikolov, a structural biologist at Memorial Sloan Kettering. "This detailed understanding of these assemblies helps us better understand neural wiring, and may one day be useful in the development of drugs to treat spinal cord or brain injuries."

In a developing nervous system, the signaling molecule, Netrin-1, identified by Rockefeller University Professor Marc Tessier-Lavigne and colleagues, can guide neurons by attracting or repulsing them. In the case of axons that cross from one side to the other, extended by so-called commissural neurons, Netrin-1 attracts them toward the middle.

With a technique that uses X-rays to visualize the structure of crystalized proteins, research scientist Kai Xu and colleagues in Nikolov's laboratory revealed that Netrin-1 has two separate binding sites on opposite ends, enabling it to simultaneously bind to different receptors. This may explain how Netrin-1, which is an important axon-guiding molecule, can affect in different ways neurons that express different combinations of receptors, Nikolov says.

For some time, scientists have known commissural neurons used the receptor molecule DCC to detect Netrin-1. Neogenin has a structure similar to DCC, and this research, described today in *Science*, confirms neogenin too acts as a sensing molecule for commissural neurons in mammals.

In experiments that complemented the structural work, conducted by Nicolas Renier and Zhuhao Wu in Tessier-Lavigne's lab, the researchers confirmed that, like DCC, neogenin senses Netrin-1 for the growing commissural neurons in mice.

These neurons are part of the system by which one side of the brain controls movement on the opposite side of the body. As a result, a mutation in the gene responsible for DCC interferes with this coordination, causing congenital mirror movement disorder. People with this disorder cannot move one side of the body in isolation; for example, a right-handed wave is mirrored by a similar gesture by the left hand.

The work also has implications for understanding why DCC, neogenin and other cell-surface receptors come in slightly different forms, called splice isoforms. The structural research revealed these isoforms bind differently to Netrin-1. However, it is not yet clear what this means for neuron wiring, Nikolov says.

"With this structural knowledge, and with the identification of an additional receptor involved in axon guidance in the spinal cord, we are gaining deeper insight into the mechanisms through which neurons make connections that produce a functioning nervous system, as well as the dysfunction that arises from miswiring of connections" says Tessier-Lavigne.

More information: Structures of netrin-1 bound to two receptors provide insight into its axon guidance mechanism, Kai Xu, Zhuhao Wu, Nicolas Renier, Alexander Antipenko, Dorothea Tzvetkova-Robev, Yan Xu, Maria Minchenko, Vincenzo Nardi-Dei, Kanagalaghatta R. Rajashankar, Juha Himanen, Marc Tessier-Lavigne and Dimitar B. Nikolov, *Science* Online: May 29, 2014

Provided by Rockefeller University