Mechanisms of brain wiring

Department of
Biological Chemistry

Dr. Avraham Yaron

Liat Haklai-Topper, Erez Romi, Guy Mlechkovich, Zohar Fridman, Adi Minis, Sheila Tiomny, Sharon Amit, Dana Savariego

☎ 972 8 934 6240

FAX 972 8 934 4118

@ avraham.yaron@weizmann.ac.il

www.weizmann.ac.il/Biological_Chemistry/scientist/Yaron/yaron.html

The brain is many times compared to a sophisticated computer, capable of fast and complicated computations that enable us to sense the world, move our body and have ideas and feelings.

Although there is much simplification in this comparison, and the brain is much beyond any computer that was ever made by man, some aspects of this comparison are true. One of them is that, in the same way as computers, the connections inside the brain need to be wired in a precise manner during development in order to ensure its proper function. What are the mechanisms that guarantee the proper wiring between the billions neurons during brain development? Axons are guided to the targets by molecules in the extracellular environment called guidance cues. These cues can be either attractive, pulling axons in the right direction; or repulsive, preventing axons from navigating to incorrect targets. Guidance cues activate receptors that reside on axons, which trigger signaling cascades that modulate the cytoskeleton and steer the axons in the right way. In addition axons have the capacity for great plasticity in their response to guidance cues. During their journey to the targets axons can lose the ability to respond to a guidance cue that they initially responded to, and acquire the ability to react to others. One of the means by which plasticity is achieved is dynamic regulation of axon guidance receptors. We are using the development of the somatosensory system in mice as a model system a number of fundamental problems in the wiring of the nervous system.

Somatosensory information from the limbs and trunk is conveyed by neurons in the dorsal root ganglia (DRG) flanking the spinal cord. Each DRG neuron has two axonal branches: one peripheral and one central. The peripheral branch projects to skin and muscle where its termini respond to sensory stimuli such as pain, temperature and position sense. The central branch projects into the spinal cord and delivers the sensory information to the central nervous system (CNS). We are using a lacZ transgene driven by a sensory neurons specific promoter to visualize the axons of the somatosensory system in vivo (Figure-1).

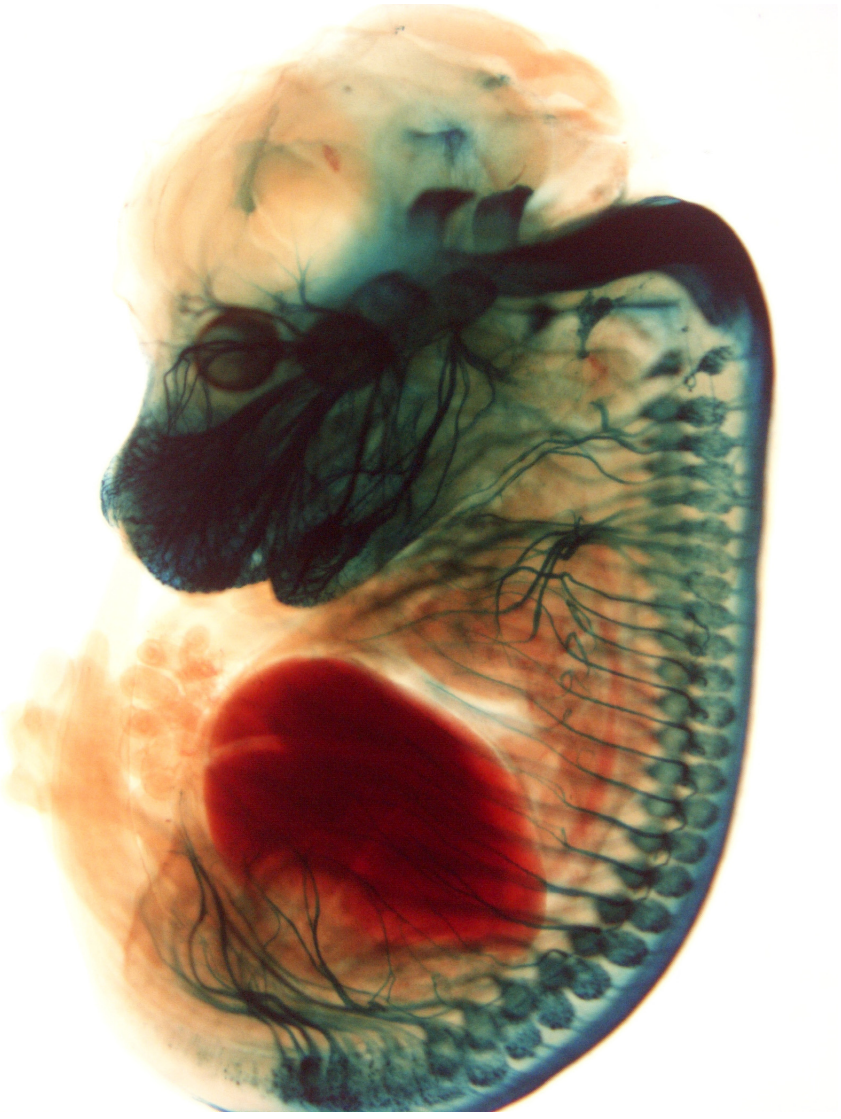

Fig. 1 Visualization of sensory axons using a whole-mount X-gal staining of an embryo harboring the Brn3a-LacZ taransgene.

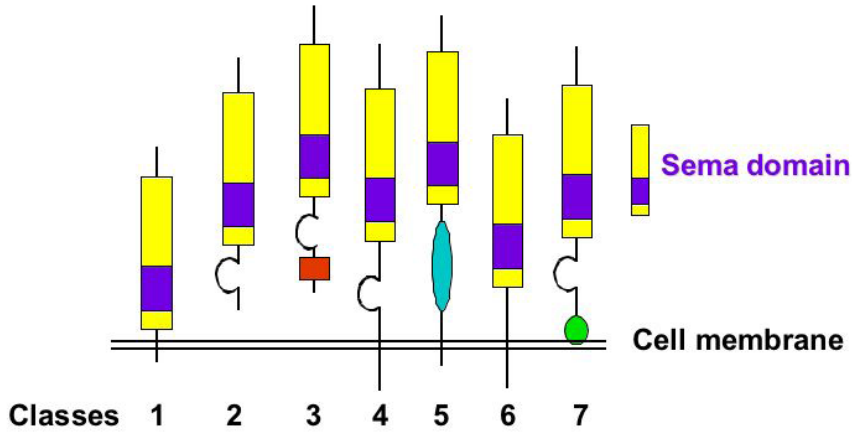

Fig. 2 Schematic representation of the Semaphorin family. The family is comprised of 23 members divided into 7 classes. Class 1-2 in invertebrates and class 3-7 in vertebrates.

One of the most important guidance cues of sensory axons is the Semaphorins family (Figure-2). The vertebrate Semaphorins are a large family, comprised of 19 secreted and membrane-bound molecules. Within this family, the six secreted proteins in class 3 are the best characterized. The receptors that mediate repulsive responses to class 3 Semaphorins have been shown to be heteromeric complexes including binding and signaling moieties. The binding moieties are members of the Neuropilin family, which comprises two members in vertebrates and are not found in invertebrates. However, both Neuropilins have very short cytoplasmic domains, suggesting that they form a complex with an additional co-receptors that functions as a signaling moiety. These co-receptors were discovered to be members of the Plexin family.

In DRG sensory neurons these Plexins were identified as Plexin-A3 and Plexin-A4.

Some of the projects in the lab include:

1. Signaling mechanisms of the class 3 Semaphorins.
2. Dynamic regulation of axonal responsiveness to the class 3 Semaphorins through proteolysis.
3. Mechanisms of axonal elimination during development

Studying the guidance mechanisms of sensory axons is of clinical importance as well. In many situations, such as diabetes or treatment with chemotherapy for cancer, a neuropathy of sensory axons develops that is manifested by disconnection of the axons from their targets, which leads to a severe pain. Currently there is no efficient treatment for this condition; moreover the reason that neuropathy arise in these situations is unclear. We believe that by understanding the mechanisms and through the identification of the molecules that are involved in the wiring of sensory axons during development we will be able to re-wire the axons to their targets, and by that, to provide a novel treatment for sensory axons neuropathy.

Selected publications

Yaron, A and Zheng, B, Navigating their way to the clinic: emerging roles for axon guidance molecules in neurological disorders and injury. Developmental Neurobiology (2007) 67:1216-1231.

Yaron, A., P-H, Huang., Cheng H-J and Tessier-Lavigne, M., Differential requirement for Plexin-A3 and -A4 in mediating responses of sensory and sympathetic neurons to distinct class 3 Semaphorins. Neuron (2005) 45:513-523.

Bagri, A., Cheng H-J., Yaron, A., Pleasure, S.J and Tessier-Lavigne, M., Stereotyped Pruning of Long Hippocampal Axon Branches Triggered by Retraction Inducers of the Semaphorin Family. Cell (2003) 13:285-299

Acknowledgements

Human Frontier Science Program - Career Development Award (CDA-24/2006-C)

INTERNAL support

Minerva Foundation, Nella and Leon Benoziyo Center for Neurological Diseases