Following direction: How neurons can tell top from bottom and front from back

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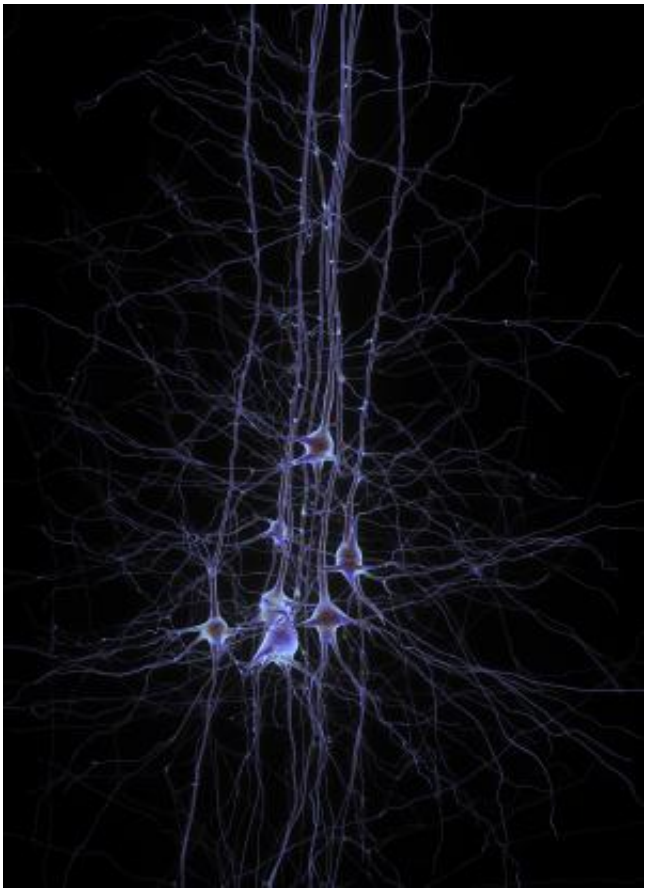

This is a group of neurons. Credit: EPFL/Human Brain Project

The question of how neurons and their axons establish spatial polarity and direction in tissues and organs is a fundamental question of any organism or biological system. Our cells and axons precisely orient

themselves in response to external cues, but what are the core pathways and how are they integrated?

Lead author Dr. Naomi Levy-Strumpf and principal investigator Dr. Joseph Culotti developed a novel conceptual framework, published on-line in *PLoS Genetics*, June 5 2014.

They investigated netrin and Wnt, signaling pathways that are implicated in cancer as well as in normal development. Working with *C. elegans*, they found that the UNC-6/netrin guidance cue, which has a conserved role in guiding cell and growth-cone migrations along the dorso-ventral axis, contributes to establishing antero-posterior polarity. Meanwhile, Wnts that are critical for determining polarity and guidance along the A/P axis are also involved in setting up polarity along the D/V axis. This provides a novel conceptual view of how A/P and D/V guidance signals are integrated intracellularly to generate polarized migration.

Redundancy goes both ways

An unexpected finding is that each pathway is redundant in both in A/P and D/V guidance, and in diverse processes that are involved in viability. "This redundancy tends to mask the roles of netrin and Wnt signaling in various biological processes," says Dr. Levy-Strumpf. "Now that we have identified the redundancy we can get a better insight into the concerted contribution of these two key signalling pathways in normal development as well as in tumor progression and metastasis." She is a research associate in the Culotti lab. Dr. Culotti is a Senior Investigator at the Lunenfeld-Tanenbaum and is a Professor of Molecular Genetics at University of Toronto.

'By means of a comprehensive genetic analysis, we found that simultaneous loss of Wnt and netrin signaling components reveals previously unknown and unexpected redundant roles for Wnt and netrin

signaling pathways in both D/V and A/P guidance of migrating cells and axons in *C. elegans*, as well as in processes essential for organ function and viability. Thus, in addition to providing polarity information for migration along the axis of their gradation, Wnts and netrin are each able to guide migrations orthogonal to the axis of their gradation.'

"These results suggest the existence of novel mechanisms for guiding cell migrations that are different from previously demonstrated mechanisms involving simple attraction toward or repulsion away from a guidance cue. Now we're trying to illuminate them," says Dr. Culotti.

"This is an excellent example of the power of genetic analysis of the worm in neurobiology," says Dr. Jim Woodgett, Director of the Lunenfeld-Tanenbaum. "The exquisite sensitivity of being able to track the migration behavior of a single neuron coupled with robust tests is simply not possible yet in mammalian models. Yet now that this pathway interaction has been shown to occur, it'll only be a matter of time for someone to replicate it in mice."

The paper, "Netrins and Wnts Function Redundantly to Regulate Antero-Posterior and Dorso-Ventral Guidance in *C. elegans*," was published online in *PLoS Genetics* on June 5, 2014. Funders include the Canadian Institutes for Health Research, Canadian Foundation for Innovation, Canada Research Chairs, and Mount Sinai Hospital Foundation.

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