Systematic exploration of transcriptional networks: putting the function in functional genomics.

Genevieve Konopka and Daniel H. Geschwind. Program in Neurogenetics, Department of Neurology, University of California, Los Angeles, California, USA.

Knowledge at the level of the genome challenges neurobiologists to move beyond the study of single genes and connect entire molecular pathways with cognitive and behavioral circuits. However, the sheer volumes of data produced using modern techniques such as microarrays or RNA-seq requires new methods to organize the data and observe the key patterns that can be difficult to discern with standard statistical analyses. Advances in network theory have shown that biological systems obey a hierarchical, scale free topology, which has significant implications for the biologist. Here, I will discuss how we have exploited this organizational principle to observe the underlying organization of the transcriptome in the brain in health and disease.

First, I will present a historical perspective on the development of tools for characterizing genes and gene expression, and provide an in-depth presentation of next generation sequencing technologies. These rapidly advancing tools are yielding unprecedented amounts of data that require creative and combinatorial approaches for mining the data for informative biological meaning. Thus, I will discuss how we have utilized multiple analytical approaches to build networks from these datasets. These networks are composed of modules of highly co-expressed genes that correspond to key functional entities, and within modules we can identify the hubs, or most central genes. We show that one can use graph theory to build networks from whole brain tissue that permits identification of the gene expression signature of individual cell types, a form of in silico dissection that does not require single cell purification or profiling. We compare insights obtained using standard analysis of differential expression in various neuronal cell types with that obtained from networks, which highlights the clear advantages of this approach to identifying the key sources of neuronal diversity. A graph theory based network approach also provides a framework for large scale meta-analysis and comparative genomics by relying on robust co-expression relationships between genes. This is especially important for cross-species or evolutionary comparisons, where rather than relying on single gene changes, we can identify robust relationships to be used as focal points for comparisons. Here, we provide examples comparing human to non-human primates, and human to mouse, both of which yield several remarkable insights that are relevant to human disease. Furthermore, I will detail how the use of such technologies and analyses have allowed us to 1) investigate networks of gene expression regulated by a single transcription factor, and 2) uncover species-specific patterns of gene expression.

Literature:


Dr. Genevieve Konopka received dual bachelor of science degrees in Biology and Brain and Cognitive Sciences from MIT in 1997. She obtained her Ph.D. in Neurobiology from Harvard University in 2004 where she worked in the laboratory of Azad Bonni studying the signaling pathways underlying astrocyte transformation. Next, she completed a Ruth L. Kirschstein National Research Service Award supported postdoctoral fellowship at the Medical College of Wisconsin where she studied the signaling pathways involved in cell adhesion under Dr. Stephen Duncan. Dr. Konopka is currently a senior postdoctoral fellow in the laboratory of Dr. Daniel Geschwind in the Neurology Department at UCLA. She is supported by the A.P. Giannini Foundation for her investigations into the signaling pathways involved in the evolution of language, and is the recipient of both an NIH Pathway to Independence Award and a NARSAD Young Investigator Award for her studies of FOXP2-regulated signaling pathways in autism and schizophrenia. The focus of her research is understanding how developmental signaling pathways are disrupted in neuropsychiatric illnesses, and identifying human-specific pathways that are vulnerable to neuropsychiatric disease. Dr. Konopka is utilizing a combination of microarrays, next generation sequencing, and cell culture and animal models to uncover the signaling networks important for higher cognitive functions.